Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 11/1/12**
(See policy history boxes for previous effective dates)

Title: Bone Marrow - Stem Cell Transplant for Waldenström's Macroglobulinemia

Description / Background

Hematopoietic Stem-Cell Transplantation
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 radiation therapy. 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 "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD). Cord blood is discussed in greater detail in policy No. 7.01.50.

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 human leukocyte antigens (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 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 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 prior to undergoing bone marrow ablation. As a consequence, autologous HSCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to 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 non-relapse mortality (NRM) 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 NRM 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 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 policy, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

Waldenstrom Macroglobulinemia

Waldenstrom macroglobulinemia (WM) is a B cell malignancy that accounts for 1–2% of hematologic malignancies, with an estimated 1,500 new cases annually in the U.S. The median age of WM patients at presentation is 63 to 68 years, with men comprising 55–70% of cases. Median survival of WM ranges from 5 to10 years, with age, hemoglobin concentration, serum albumin level and beta-2 microglobulin level as predictors of outcome. The Revised European American Lymphoma (REAL) and World Health Organization (WHO) classification, and a consensus group formed at the Second International Workshop on WM 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 no minimum serum concentration of IgM is necessary for a diagnosis of WM.

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 hemoglobin concentration less than 100 g/L; platelet count less than 100 x 10^9/L; 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 have included alkylating agents (chlorambucil, cyclophosphamide, melphalan), purine analogues (cladribine, fludarabine), and monoclonal antibody agents (rituximab), alone or in various combinations. Plasma exchange is indicated for acute treatment of symptomatic hyperviscosity.

Medical Policy Statement

Autologous hematopoietic stem-cell transplantation is established as salvage therapy of chemosensitive Waldenström's macroglobulinemia. It is a useful therapeutic option when indicated.

Allogeneic hematopoietic stem-cell transplantation is considered experimental and investigational to treat Waldenström's macroglobulinemia. It has not been shown to improve clinical outcomes better than established therapies.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions:
Autologous hematopoietic stem-cell transplantation for chemosensitive Waldenström's macroglobulinemia patients who have relapsed after initially responding to treatment, including chemotherapy, alone or in various combinations, with agents such as:

- Alkylating agents (chlorambucil, cyclophosphamide, melphalan)
- Purine analogues (cladribine, fludarabine)
- Monoclonal antibody agents (rituximab)

Relative contraindications:
The selection process for approved tissue transplants is designed to obtain the best result for each patient. Therefore, relative contraindications to HSCT may include, but are not limited to:

- Poor cardiac function: Ejection fraction should be greater than 45% with no overt symptoms of congestive heart failure.
- Poor pulmonary function: Pulmonary function tests must be greater than or equal to 50% of predicted value.
- Poor renal function: Renal creatinine clearance should be greater than 40 ml/min or creatinine must be less than or equal to 2mg/dl.
- Poor liver function: There should be no history of severe chronic liver disease
- Presence of HIV or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus (HTLV-1).

Exclusions:
Allogeneic hematopoietic stem-cell transplantation for Waldenström's macroglobulinemia.

CPT / HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

38204	38205	38206	38208	38209	38210
38211	38212	38213	38214	38215	38220
38221	38230	38232	38240	38241	38242

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

A 2002 International Workshop summarized clinical experience (combined n=49) using autologous hematopoietic stem-cell transplantation (HSCT) for Waldenström's macroglobulinemia (WM). (1) These were all small feasibility studies that reported response rates but lacked data on survival and other long-term outcomes. A total of 9 (18%) achieved complete response (CR) and 39 (80%) achieved partial response (PR), but data on the durability of these responses were unavailable.

A consensus panel from the Second International Workshop on Waldenström's Macroglobulinemia recommended that autologous HSCT may be considered for selected patients with refractory or relapsing disease, but allogeneic transplants should be used only in the context of a clinical trial. (2) Another recent review agreed that the role of autologous HSCT for Waldenstrom macroglobulinemia was not fully defined, although its empirical use might be appropriate for some patients with relapsed or refractory disease. (3) This review also considered allogeneic transplants for Waldenstrom macroglobulinemia to be investigational therapy.

In 2004, a consensus panel from the Third International Workshop on Waldenström's Macroglobulinemia suggested autologous HSCT may be considered for eligible patients with primary refractory or relapsing disease but that allogeneic transplants should be cautiously approached, only in the context of a clinical trial. (4) However, the review article does not cite evidence to support the recommendations. The panelists also concluded that it was not possible to recommend a particular first-line therapeutic approach; rather, the choice should be made on the basis of individual patient considerations. A retrospective Center for International Blood and Marrow Transplant Research (CIBMTR) registry analysis of HSCT (autologous, n=10, allogeneic, n=26) for WM reported 3-year overall survival (OS) rates of 46% (95% confidence interval [CI]: 27–65%) for allogeneic HSCT recipients and 70% (95% CI: 40–93%) for autologous HSCT patients. (5) Although the CIBMTR results appear favorable, it should be noted that patients in this report were heavily pretreated, highly heterogeneous in terms of disease characteristics and risk factors, and received a variety of conditioning regimens, including myeloablative and reduced-intensity conditioning (RIC), between 1986 and 2002. These data, taken together, are insufficient to form conclusions about the potential clinical efficacy of HSCT for Waldenstrom macroglobulinemia. Subsequent additional review articles are in general agreement with this position. (6, 7)

Kyriakou et al. reported on 158 adult patients with Waldenstrom macroglobulinemia reported to the European Group for Blood and Marrow Transplantation (EBMT) between January 1991 and December 2005. (8) Median time from diagnosis to autologous HSCT was 1.7 years (range, 0.3 to 20.3 years), 32% of the patients experienced treatment failure with at least 3 of therapy, and 93% had sensitive disease at the time of HSCT. Median follow-up for surviving patients was 4.2 years (range: 0.5 to 14.8 years). Non-relapse mortality (NRM) was 3.8% at 1 year. Relapse rate was 52.1% at 5 years. Progression-free survival (PFS) and OS were 39.7% and 68.5%, respectively, at 5 years and were significantly influenced by number of lines of therapy and chemo-refractoriness at HSCT. The authors conclude that autologous HSCT is a feasible procedure in young patients with advanced Waldenstrom macroglobulinemia but that it should not be offered to patients with chemoresistant disease and to those who received more than 3 lines of therapy.

Kyriakou and colleagues also reported on a retrospective analysis of a smaller group of patients who had allogeneic HSCT for Waldenstrom macroglobulinemia. (9) A total of 86 patients received allogeneic HSCT by using either myeloablative conditioning (MAC; n=37) or reduced-intensity conditioning (RIC; n=49) regimens. The median age was 49 years (range: 23 to 64 years); 47 patients had received 3 or more previous lines of therapy, and 8 patients had experienced failure on a prior autologous HSCT. A total of 59 patients (68.6%) had chemotherapy-sensitive disease at the time of allogeneic SCT. Median follow-up of the surviving patients was 50 months. The overall response rate was 75.6%. The relapse rates at 3 years were 11% for MAC and 25% for RIC. Overall survival at 5 years was 62% for MAC and 64% for RIC, respectively. The occurrence of chronic graft-versus-host disease (GVHD) was associated with a lower relapse rate. The authors concluded that allogeneic SCT can induce durable remissions in a selected population of young and heavily pretreated patients who have Waldenström's macroglobulinemia.

Little additional published evidence is available on use of autologous HSCT for WM, as summarized in 2 recent review articles.(10, 11) No randomized trials have been reported.

Summary
In summary, based on the literature and clinical input, autologous HSCT may be considered medically necessary as salvage therapy for chemosensitive Waldenstrom macroglobulinemia. Allogeneic HSCT for Waldenstrom macroglobulinemia is considered investigational.

National Comprehensive Cancer Network Guidelines
The 2011 National Comprehensive Cancer Network (NCCN) guidelines indicate that selected cases of Waldenström's macroglobulinemia may be treated with autologous or allogeneic HSCT, but the latter only in a clinical trial. (12)

National Cancer Institute Physician Data Query (PDQ®) Database
No current study is specifically focused on HSCT for Waldenström's macroglobulinemia. Five Phase III studies are active that may involve patients with WM (Available online at: http://www.cancer.gov/clinicaltrials/search/results?protocolsearchid=10076025).

Government Regulations
National and Local:
The Medicare NCD on stem cell transplantation does not address the use of stem cell transplantation for Waldenström's macroglobulinemia specifically. However, Waldenström's

macroglobulinemia (WM) is a rare, (slow-growing) non-Hodgkin lymphoma which is also called lymphoplasmacytic lymphoma. Under Medicare, AuSCT (autologous stem cell transplant) is considered reasonable and necessary for patients with resistant non-Hodgkin's lymphomas or those presenting with poor prognostic features following an initial response.

Michigan Department of Community Health:

Medicaid covers autologous stem cell transplant following Medicare guidelines; preauth is required. Heart, bone marrow, liver, lung, simultaneous pancreas/kidney and pancreas transplants are reimbursed at the hospital's Medicaid cost to charge ratio.

- Organ acquisition costs are reimbursed at 100 percent of charges when billed using either revenue code 0811 or 0812. This applies to heart, kidney, liver, lung, simultaneous pancreas/kidney or pancreas transplants. This does not apply to bone marrow transplants. All bone marrow transplant charges are reimbursed at the hospital's cost to charge ratio.
- The letter of authorization for the transplant from the Office of Medical Affairs (OMA) or MHP must be attached to all transplant claims, otherwise, payment is denied.
- Indicate "PA letter submitted" in the Remarks Section of the submitted claim.
- For other transplant services not described by a specific DRG, identify in the Remarks Section the type of transplant that has been performed (i.e., small bowel transplant).
- If the donor and beneficiary are both Medicaid eligible, the services must be billed under each beneficiary's respective ID Number. If only the beneficiary is Medicaid eligible, bill services for both donor and beneficiary under the Medicaid beneficiary's ID Number. All other insurance resources must be exhausted before Medicaid is billed. If Medicare eligibility is denied, the denial notice must be submitted with the claim

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Bone Marrow – Stem Cell Transplantation for Acute Lymphoblastic Leukemia
- Bone Marrow – Stem Cell Transplantation for Acute Myeloid Leukemia
- Bone Marrow – Stem Cell Transplantation for Autoimmune Diseases
- Bone Marrow – Stem Cell Transplantation for Breast Cancer
- Bone Marrow – Stem Cell Transplantation for Chronic Lymphocytic Leukemia and small Cell Lymphocytic Lymphoma
- Bone Marrow – Stem Cell Transplantation for Chronic Myelogenous Leukemia
- Bone Marrow – Stem Cell Transplantation for CNS Embryonal Tumors and Ependymoma
- Bone Marrow – Stem Cell Transplantation for Epithelial Ovarian Cancer
- Bone Marrow – Stem Cell Transplantation for Genetic Diseases and Acquired Anemias
- Bone Marrow – Stem Cell Transplantation for Hodgkin Lymphoma
- Bone Marrow – Stem Cell Transplantation for Malignant Astrocytomas and Gliomas
- Bone Marrow – Stem Cell Transplantation for Miscellaneous Solid Tumors in Adults
- Bone Marrow – Stem Cell Transplantation for Multiple Myeloma
- Bone Marrow – Stem Cell Transplantation for Non-Hodgkin Lymphoma
- Bone Marrow – Stem Cell Transplantation for Primary Amyloidosis
- Bone Marrow – Stem Cell Transplantation for Solid Tumors of Childhood

- Bone Marrow – Stem Cell Transplantation for the Treatment of Germ-Cell Tumors

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References

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2. Gertz MA, Anagnostopoulos A, Anderson K et al. Treatment recommendations in Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenström's Macroglobulinemia. Semin Oncol 2003; 30(2):121-6.
3. Ghobrial IM, Gertz MA, Fonseca R. Waldenström's macroglobulinemia. Lancet Oncol 2003; 4(11):679-85.
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9. Kyriakou C, Canals C, Cornelissen JJ et al. Allogeneic stem-cell transplantation in patients with Waldenström's macroglobulinemia: report from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 2010; 28(33):4926-34.
10. Gertz MA, Reeder CB, Kyle RA et al. Stem cell transplant for Waldenström's macroglobulinemia: an underutilized technique. Bone Marrow Transplant 2011 [Epub ahead of print].
11. Usmani S, Sexton R, Crowley J et al. Autologous stem cell transplantation as a care option in Waldenström's macroglobulinemia. Clin Lymphoma Myeloma Leuk 2011; 11(1):139-42.
12. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma (V.2.2011). Available online at: http://wwwnccnorg/professionals/physician_gls/PDF/waldenstromspdf Last accessed May 2012, 2011.
13. Blue Cross Blue Shield Association. Hematopoietic Stem-Cell Transplantation for Waldenstrom Macroglobulinemia. Medical Policy Reference Manual. Policy #8.01.54, Issue 2:2012, original policy date 2/10/11, last review date 2/9/12.
14. Centers for Medicare & Medicaid Services (CMS), *Medicare Coverage Database*, "Bone Marrow or Stem Cell Transplantation," subject number HONC-009, Contractor Name-Wisconsin Physicians Service (WPS), existing policy date 11/01/2010.
15. Centers for Medicare and Medicaid Services (CMS), *Medicare Coverage Database*, National Coverage Determination (NCD) for Stem Cell Transplantation (110.8.1), effective date of revision 8/4/10, available at < http://www.cms.gov/medicare-coverage-database/details/ncd-

details.aspx?NCDId=45&ncdver=5&NCAId=238&ver=12&NcaName=Allogeneic+Hematopoietic+Stem+Cell+Transplantation+(HSCT)+for+Myelodysplastic+Syndrome&bc=BEAAAAAAEAAA& >, (May 29, 2012).
16. HAYES Medical Technology Directory. Nonmyeloablative Transplantation for Hematological Malignancies. Lansdale, PA: HAYES, Inc. February 28, 2006, Archived March 28, 2011, outdated.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 5/29/12, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/11	3/17/11	3/3/11	Joint policy established. Information previously available on the following policies: • Allogeneic BMT-Established • Allogeneic BMT – Investigational • Autologous BMT – Established • Autologous BMT – Investigational
11/1/12	8/21/12	8/21/12	Policy title changed from, "Bone Marrow/Stem-Cell Transplantation for Primary Amyloidosis or Waldenström's Macroglobulinemia" to "Bone Marrow/Stem-Cell Transplantation for Waldenström's Macroglobulinemia" (separate policy). No change in policy status.

Next Review Date: 3rd Qtr, 2013

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: BONE MARROW TRANSPLANT FOR WALDENSTRÖM'S MACROGLOBULINEMIA

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	Covered; criteria apply.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.
Blue Cross Complete of Michigan	Covered; criteria apply.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.