

Corporate Medical Policy

Hematopoietic Stem-Cell Transplantation for Waldenstrom Macroglobulinemia

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Description of Procedure or Service

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).

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

Hematopoietic Stem-Cell Transplantation for Waldenstrom Macroglobulinemia

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 to 10 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 $100 \times 10^9/L$; 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.

Related Policies:

Hematopoietic Stem-Cell Transplantation for Non-Hodgkin Lymphomas

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Hematopoietic Stem-Cell Transplantation for Waldenstrom Macroglobulinemia

Policy

BCBSNC will provide coverage for hematopoietic stem-cell transplantation for Waldenstrom Macroglobulinemia when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Some patients may be eligible for coverage under Clinical Trials. Refer to the policy on Clinical Trial Services for Life-Threatening Conditions.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Hematopoietic Stem-Cell Transplantation for Waldenstrom Macroglobulinemia is covered

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

When Hematopoietic Stem-Cell Transplantation for Waldenstrom Macroglobulinemia is not covered

Allogeneic hematopoietic stem-cell transplantation is considered investigational to treat Waldenstrom macroglobulinemia. BCBSNC does not cover investigational services.

Policy Guidelines

A literature search through December 2010 identified the following relevant studies.

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. 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 three 3 of therapy, and 93% had sensitive disease at the time of SCT. Median follow-up for surviving patients was 4.2 years (range: 0.5 to 14.8 years). Nonrelapse mortality 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 chemorefractoriness 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. 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

Hematopoietic Stem-Cell Transplantation for Waldenstrom Macroglobulinemia

survival at 5 years was 62% for MAC and 64% for RIC, respectively. The occurrence of chronic graft-versus-host (GVH) disease 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 Waldenstrom macroglobulinemia.

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

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 38205, 38206, 38230, 38232, 38240, 38241, 38242, S2150

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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* 2010; 28(13):2227-32.

Kyriakou C, Canals C, Cornelissen JJ et al. Allogeneic stem-cell transplantation in patients with Waldenström macroglobulinemia: report from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol* 2010; 28(33):4926-34.

National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma (V.1.2011). Available online at: http://www.nccn.org/professionals/physician_gls/PDF/waldenstroms.pdf.

BCBSA Medical Policy Reference Manual [Electronic Manual]. 8.01.54, 2/10/2011

Medical Director – 4/2011

Specialty Matched Consultant Advisory Panel – 11/2011

Policy Implementation/Update Information

5/10/11 New policy created (Waldenstrom macroglobulinemia removed from original policy entitled Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis or Waldenstrom Macroglobulinemia.) "Autologous hematopoietic stem-cell transplantation may be considered medically necessary as salvage therapy of chemosensitive Waldenstrom macroglobulinemia." Medical Director review 4/28/2011. (btw)

1/10/12 Specialty Matched Consultant Advisory Panel review 11/30/11. No change to policy

Hematopoietic Stem-Cell Transplantation for Waldenstrom Macroglobulinemia

intent. (btw)

2/21/12 Added new 2012 CPT code, 38232, to Billing/Coding section. (btw)

5/1/12 Reference added. (btw)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.