Hematopoietic Stem-Cell Transplantation for Waldenstrom Macroglobulinemia

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Line(s) of Business: HMO; PPO
Current Effective Date: 04/26/2013
Section: Transplants
Place(s) of Service: Outpatient; Inpatient

Precertification is required for this service.

I. Description

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 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 x 109/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.

II. Policy

A. Autologous hematopoietic stem-cell transplantation is covered (subject to Limitations/Exclusions and Administrative Guidelines) as salvage therapy of chemosensitive Waldenstrom macroglobulinemia.

B. Allogeneic hematopoietic stem-cell transplantation is not covered to treat Waldenstrom macroglobulinemia as it is not known to be effective in improving health outcomes.

III. Policy Guidelines

In 2003, CPT centralized codes describing allogeneic and autologous HSCT services to the hematology section (38204-38242). Not all codes are applicable for each stem-cell transplant procedure. For example, Plans should determine if cryopreservation is performed. A range of codes describes services associated with cryopreservation, storage, and thawing of cells (38208-38215).

CPT 38208 and 38209 describe thawing and washing of cryopreserved cells
CPT 38210-38214 describe certain cell types being depleted
CPT 38215 describes plasma cell concentration

IV. Limitations/Exclusions

The patient must be an appropriate candidate for transplant. This is defined as:

A. Adequate cardiopulmonary status
B. Absence of active infection
C. No history of malignancy within 5 years of transplantation, excluding nonmelanomatous skin cancers
D. Documentation of patient compliance with medical management
V. Administrative Guidelines

Precertification is required for a transplant evaluation and for the transplant itself and should be submitted by the proposed treating facility. To precertify, please complete HMSA's Precertification Request and mail or fax the form as indicated along with the required documentation.

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic</td>
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<tr>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, autologous</td>
</tr>
<tr>
<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest without washing, per donor</td>
</tr>
<tr>
<td>38209</td>
<td>;thawing of previously frozen harvest, with washing, per donor</td>
</tr>
<tr>
<td>38210</td>
<td>;specific cell depletion with harvest, T-cell depletion</td>
</tr>
<tr>
<td>38211</td>
<td>;tumor-cell depletion</td>
</tr>
<tr>
<td>38212</td>
<td>;red blood cell removal</td>
</tr>
<tr>
<td>38213</td>
<td>;platelet depletion</td>
</tr>
<tr>
<td>38214</td>
<td>;plasma (volume) depletion</td>
</tr>
<tr>
<td>38215</td>
<td>;cell concentration in plasma, mononuclear, or buffy coat layer</td>
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<tr>
<td>38220</td>
<td>Bone marrow; aspiration only</td>
</tr>
<tr>
<td>38221</td>
<td>Biopsy, needle or trocar</td>
</tr>
<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
</tr>
<tr>
<td>38240</td>
<td>Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor</td>
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<tr>
<td>38241</td>
<td>;autologous transplantation</td>
</tr>
<tr>
<td>38242</td>
<td>Allogeneic lymphocyte infusions</td>
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<tr>
<td>38243</td>
<td>;HPC boost</td>
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<tr>
<th>ICD-9 Procedure Codes</th>
<th>Description</th>
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<tr>
<td>41.01</td>
<td>Autologous bone marrow transplant without purging</td>
</tr>
<tr>
<td>41.02</td>
<td>Allogeneic bone marrow transplant with purging</td>
</tr>
<tr>
<td>41.03</td>
<td>Allogeneic bone marrow transplant without purging</td>
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### Scientific Background

A 2002 International Workshop summarized clinical experience (combined n=49) using autologous hematopoietic stem-cell transplantation (HSCT) for Waldenstrom 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 Waldenstrom’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 Waldenstrom’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). Nonrelapse 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 chemoresistance 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 Waldenstrom macroglobulinemia.

Little additional published evidence is available on use of autologous HSCT for WM, as summarized in 2 recent review articles.(10-13) No randomized trials have been reported.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

In response to requests, input was received from no physician specialty societies and 5 academic medical centers, including 3 transplant centers, while this policy was under review in 2011. 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. The input indicated that autologous HSCT may be considered medically necessary as salvage therapy in Waldenstrom macroglobulinemia that is chemosensitive. The input was mixed for use of allogeneic HSCT, with comments about this being performed as part of a clinical trial.

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 2013 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. (14)

National Cancer Institute Physician Data Query (PDQ®) Database

No current study is specifically focused on HSCT for Waldenstrom’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).

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.
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This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VIII. References
