Hematopoietic Stem-Cell Transplantation for Waldenstrom Macroglobulinemia

Policy Number: 8.01.54  Last Review: 6/2017

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for hematopoietic stem-cell transplantation for Waldenstrom macroglobulinemia when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Autologous hematopoietic stem-cell transplantation may be considered medically necessary as salvage therapy of chemosensitive Waldenstrom macroglobulinemia.

When Policy Topic is not covered
Allogeneic hematopoietic stem-cell transplantation is considered investigational to treat Waldenstrom macroglobulinemia.

Considerations
In 2003, CPT centralized codes describing allogeneic and autologous hematopoietic cell transplantation 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 (38207-38215).

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.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
</tbody>
</table>
• With Waldenström | | | • Overall survival |
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 a separate policy.

For individuals who have Waldenström macroglobulinemia 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 Waldenström macroglobulinemia. Analyses of registry data have found overall survival rates of 52% at 5 years 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.

Clinical input and national and international clinical guidelines support the use of autologous HCT as salvage therapy for chemosensitive Waldenström macroglobulinemia. Allogeneic HCT is recommended in the context of clinical trials. Thus, autologous HCT may be considered medically necessary as salvage therapy for chemosensitive Waldenström macroglobulinemia and allogeneic HCT for Waldenström macroglobulinemia is considered investigational.

**Background**

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. The median age of WM patients at presentation 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 β₂-microglobulin level as predictors of outcome. The Revised European American Lymphoma (REAL) 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 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 (eg, 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 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.

**Rationale**

This evidence review was originally created in February 2011 and has been updated regularly with searches of the MEDLINE database. The most recent literature review was through October 26, 2016. Following is a summary of key literature to date.

**Hematopoietic Cell Transplantation for Waldenström Macroglobulinemia**

Few published data are available and there is a lack of studies comparing hematopoietic cell transplantation (HCT) to other treatments (eg, chemotherapy) in patients with Waldenström macroglobulinemia (WM). Several retrospective series have been published.

**Autologous HCT**

In 2010, Kyriakou et al evaluated on 158 adult patients with WM reported to the European Group for Blood and Marrow Transplantation between January 1991 and December 2005. Median time from diagnosis to autologous HCT was 1.7 years (range, 0.3-20.3 years); 32% of the patients experienced treatment failure with at least 3 lines of therapy; and 93% had sensitive disease at the time of HCT. Median follow-up for surviving patients was 4.2 years (range, 0.5-14.8 years). Nonrelapse mortality (NRM) was 3.8% at 1 year. Relapse rate was 52.1% at 5 years. Progression-free survival and overall survival (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 HCT. Authors concluded that autologous HCT is a feasible procedure in young patients with advanced WM but that it should not be offered to patients with chemoresistant disease or to those who have received more than 3 lines of therapy.

**Allogeneic HCT**

Data from the Center for International Blood and Marrow Transplant Research registry have been published periodically, most recently in 2016. Cornell et al (2016) reported retrospectively on 144 adult patients entered in the registry
between 2001 and 2013 who underwent allogeneic HCT. Patients had relapsed after receiving at least 1 line of prior therapy. Hematopoietic cells were obtained from human leukocyte antigen–matched or –mismatched donors; cord blood stem cells were excluded. A total of 67 patients received myeloablative conditioning and 67 received reduced-intensity conditioning (RIC). Over half of patients (n=82 [57%]) had chemosensitive disease. OS rates were 74% at 1 year and 52% at 5 years. Patients with chemosensitive disease had significantly better 1- and 5-year OS rates compared to patients with chemo-resistant disease.

In 2010, Kyriakou et al also retrospectively analyzed data on 86 who had allogeneic HCT for WM. Patients had either myeloablative conditioning (MAC; n=37) or RIC (n=49) regimens. Median age was 49 years (range, 23-64 years); 47 patients had received 3 or more previous lines of therapy; and 8 patients had experienced failure on a prior autologous HCT. Fifty-nine (68.6%) patients had chemo-sensitive disease at the time of allogeneic HCT. Median follow-up of the surviving patients was 50 months. The overall response rate was 75.6%. Relapse rates at 3 years were 11% for MAC and 25% for RIC. OS at 5 years was 62% for MAC and 64% for RIC. The occurrence of chronic graft-versus-host disease was associated with a lower relapse rate.

Section Summary: Hematopoietic Cell Transplantation for Waldenström Macroglobulinemia
Several retrospective series have evaluated HCT for WM. Analyses of registry data found OS rates of 52% at 5 years after allogeneic HCT and 68.5% after autologous HST. The total number of patients studied was small and there is a lack of published controlled studies.

Summary of Evidence
For individuals who have Waldenström macroglobulinemia who receive hematopoietic cell transplantation (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 Waldenström macroglobulinemia. Analyses of registry data have found overall survival rates of 52% at 5 years 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.

Supplemental Information
Clinical Input 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 5 academic medical centers, including 3 transplant centers, while this policy was under review in 2011. The input indicated that autologous hematopoietic cell transplantation (HCT) may be considered medically necessary as salvage therapy in Waldenström macroglobulinemia that is chemosensitive. The input was mixed on use of allogeneic HCT, with comments about this being performed as part of a clinical trial.

**Practice Guidelines and Position Statements**

**National Comprehensive Cancer Network**

National Comprehensive Cancer Network (NCCN) guidelines on Waldenström macroglobulinemia (WM) and lymphoplasmacytic lymphoma (v.2.2016) indicate that, for patients 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).\(^4\) NCCN stated that allogeneic cell transplantation “may be considered, but preferably in the context of a clinical trial.”

**Eighth International Workshop on Waldenström’s Macroglobulinemia**

In 2016, consensus recommendations from the Eighth International Workshop on Waldenström’s Macroglobulinemia were published.\(^5\) The panel concluded that autologous hematopoietic cell transplantation (HCT) is a treatment option for high-risk WM patients who are eligible for transplant. It further stated that autologous HCT should be offered at early relapses and is not as beneficial once patients have been exposed to more than 3 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.”

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 1.

**Table 1. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrolment</th>
<th>Completion Date</th>
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<tr>
<td>Ongoing</td>
<td></td>
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<tr>
<td>NCT02844361</td>
<td>Comparison of ASCT and Conventional Chemotherapy in High Risk Waldenström Macroglobulinemia (BDH-WM03)</td>
<td>70</td>
<td>May 2020</td>
</tr>
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</table>

NCT: national clinical trial.
References

Billing Coding/Physician Documentation Information
38204 Management of recipient hematopoietic progenitor cell donor search and cell acquisition
38205 Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogenic
38206 Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207 Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208 Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing
38209 Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
38210 Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211 Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212 Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213 Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214 Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215 Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38220 Bone marrow; aspiration only
38221 Bone marrow; biopsy, needle or trocar
38230 Bone marrow harvesting for transplantation; allogeneic
38232 Bone marrow harvesting for transplantation; autologous
38240 Bone marrow or blood-derived peripheral stem cell transplantation; allogenic
38241 Bone marrow or blood-derived peripheral stem cell transplantation; autologous

38242 Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions

S2140 Cord blood harvesting for transplantation, allogeneic

S2142 Cord blood-derived stem

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 services; and the number of days pre- and post-transplant care in the global definition

ICD-10 Codes

C88.0 Waldenstrom macroglobulinemia

Additional Policy Key Words

N/A

Policy Implementation/Update Information

12/1/11 New policy created (Waldenstrom macroglobulinemia removed from original policy No. 8.01.42 [previously combined amyloidosis and Waldenstrom policy]). Policy statement changed to indicate autologous SCT may be considered medically necessary as salvage therapy for chemosensitive Waldenstrom macroglobulinemia.

6/1/12 No policy statement changes.

6/1/13 No policy statement changes.

6/1/14 Added cpt 38230, 38232. No policy statement changes.

6/1/15 No policy statement changes.

6/1/16 No policy statement changes.

6/1/17 No policy statement changes.

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