Hematopoietic Cell Transplantation for Primary Amyloidosis or Waldenstrom’s Macroglobulinemia

Policy # 00138
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When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
• Benefits are available in the member’s contract/certificate, and
• Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider autologous hematopoietic cell transplantation (HCT) to treat primary systemic amyloidosis to be eligible for coverage.

Based on review of available data, the Company may consider autologous hematopoietic cell transplantation (HCT) as salvage therapy of chemosensitive Waldenstrom’s macroglobulinemia (WM) to be eligible for coverage.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers allogeneic hematopoietic cell transplantation (HCT) to treat primary systemic amyloidosis to be investigational.*

Based on review of available data, the Company considers allogeneic hematopoietic cell transplantation (HCT) to treat Waldenstrom’s macroglobulinemia (WM) to be investigational.*

Background/Overview
Primary Amyloidosis
The primary amyloidoses comprise a group of diseases with an underlying clonal plasma cell dyscrasia. They are characterized by the extracellular deposition of pathologic, insoluble protein fibrils with a beta-pleated sheet configuration that exhibit a pathognomonic red-green birefringence when stained with Congo red dye and examined under polarized light. These diseases are classified by the type of amyloidogenic protein involved and by the distribution of amyloid deposits. In systemic amyloidosis, the unnatural protein is produced at a site that is remote from the site(s) of deposition, whereas in localized disease, the amyloid light chain protein is produced at the site of deposition. Primary or amyloid light chain amyloidosis, the most common type of systemic amyloidosis, has an incidence similar to that of Hodgkin lymphoma or chronic myelogenous leukemia, estimated at 5 to 12 people per million annually. The median age at diagnosis is 60 years. The amyloidogenic protein in primary amyloidosis is an immunoglobulin light chain or light chain

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fragment produced by a clonal population of plasma cells in the bone marrow. While the plasma cell burden in primary amyloidosis is typically low, ranging from 5% to 10%, this disease also may occur in association with multiple myeloma in 10% to 15% of patients. Deposition of primary amyloidogenic proteins causes organ dysfunction, most frequently in the kidneys, heart, and liver, although the central nervous system and brain may be affected.

**Treatment**

Historically, this disease has had a poor prognosis, with a median survival from diagnosis of approximately 12 months, although outcomes have improved with combination chemotherapy using alkylating agents and autologous hematopoietic cell transplantation (HCT). Emerging approaches include the use of immunomodulating drugs (eg, thalidomide, lenalidomide) and the proteasome inhibitor bortezomib. Regardless of the approach, treatment of primary amyloidosis aims at rapidly reducing the production of amyloidogenic monoclonal light chains by suppressing the underlying plasma cell dyscrasia, with supportive care to decrease symptoms and maintain organ function. The therapeutic index of any chemotherapy regimen is a key consideration in the context of underlying organ dysfunction.

**Hematopoietic Cell Transplantation**

HCT refers to the infusion of hematopoietic stem cells to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naive” and thus are associated with a lower incidence of rejection or graft-versus-host disease.

**Autologous HCT**

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. The success of autologous HCT 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 before undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient’s disease is in complete response. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

**Allogeneic HCT**

Immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing human leukocyte antigen (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.
The conventional ("classical") practice of allogeneic HCT involves administration of cytotoxic agents (eg, 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 the patient's bone marrow space. While the slower graft-versus-malignancy 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 events 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 HCT, immune suppressant drugs are required to minimize graft rejection and graft-versus-host disease, which also increases susceptibility to opportunistic infections.

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 and to minimize as much as possible 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 variable 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.

Waldenstrom’s 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 β2-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 IgM-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 HCT**

The conventional (“classical”) practice of allogeneic HCT involves administration of cytotoxic agents (eg, 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.

Rationale/Source

Primary Amyloidosis

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice. The following is a summary of key literature to date.

PRIMARY AMYLOIDOSIS

Chemotherapy for the treatment of light chain amyloidosis was introduced in 1972 in the form of melphalan and prednisone. This chemotherapy regimen has yielded higher response and longer survival rates than colchicine or prior therapies. Survival after oral melphalan with prednisone (typically 12-18 months) is longer...
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than for untreated patients or those given older therapies (10-14 months), but more effective regimens have been sought. Combination therapy with vincristine, doxorubicin, and dexamethasone, a well-established regimen for myeloma, has been investigated. However, because of its toxicity, vincristine, doxorubicin, and dexamethasone therapy usually is limited to patients without peripheral neuropathy or cardiomyopathy, both common complications of amyloidosis.

Because conventional regimens rarely cure systemic amyloidosis, and because of the close biologic similarity to multiple myeloma, myeloablative chemotherapy with autologous hematopoietic stem transplantation (HCT) is being investigated for this disease.

Autologous HCT

Initial results of autologous HCT in uncontrolled patient series were published in 1998. Clinical response rates (50%-60%) were nearly twice those reported for conventional therapy, and 2-year survival ranged from 56% to 68%. Kaplan-Meier analysis of a 2004 matched comparison study (63 pairs) showed greater overall survival (OS) for those given autotransplants (71% at 4 years) than for patients who were eligible for transplantation but managed conventionally (41%; p=0.004).7 However, procedure-related mortality rates of 15% to 43% were substantially higher than those observed in myeloma patients, usually in cases involving more than 2 organ systems or symptomatic cardiac involvement.

Randomized Controlled Trials

One randomized multicenter trial (2007) from the Myelome Autogreffe and Intergroupe Francophone du Myelome Intergroup compared conventional chemotherapy (melphalan plus dexamethasone, n=50) with myeloablative melphalan followed by autologous HCT (n=50). Randomization was stratified by age (<65 years or ≥65 years) and the affected organ system (cardiac, renal, neurologic, other). Of note, approximately two-thirds of patients had two or more organs affected. Hematopoietic stem cells were obtained from peripheral blood following granulocyte colony-stimulating factor mobilization. According to intention-to-treat analysis, the hematologic response rate did not differ between groups, with 12 complete responses (CR; 24%) and 14 partial responses (28%) in the chemotherapy recipients vs 11 CR (22%) and 7 partial responses (14%) in the HCT group (p=0.11). At a median follow-up of 24 months, 20 patients in the chemotherapy group had died vs 31 in the autologous HCT group. Among 65 patients who could be evaluated, the intention-to-treat median survival for patients assigned to chemotherapy was 56.9 months vs 22.2 months in the autologous HCT group (p=0.04). Analysis of patients who survived for at least 6 months and who received their assigned treatment showed no significant difference in survival rates between treatments.

Although this RCT suggested that autologous HCT may be no more efficacious than conventional chemotherapy in prolonging survival, the results were limited by the proportion of patients not receiving treatment. Among 50 patients assigned to autologous HCT, 13 (26%) did not receive the planned treatment (1 declined, 2 had insufficient stem cell harvest, 10 died before treatment), while 7 (14%) of 50 assigned to
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chemotherapy did not receive planned treatment (5 died before treatment, 1 did not tolerate treatment, 1 received incorrect treatment).

Nonrandomized Comparative Studies
A retrospective comparative analysis from a single treatment center published in 2014 provides long-term evidence for improved survival among patients with amyloid light chain amyloidosis who underwent autologous HCT compared with conventional therapies (CTR). Patients underwent autologous HCT (n=80) or CTR (n=65) following induction therapy. Patients were heterogeneous concerning age, organ involvement, cardiac involvement, renal involvement, and percent of bone marrow blast cells; all were significantly overrepresented in the CTR group compared with the HCT group. Median follow-up was 3 years for the entire cohort, with some survivors followed for up to 14 years postdiagnosis. Median 5-year survival was 63% in the HCT group compared with 38% in the CTR group (p<0.001); median survival at 10 years was 56% in the HCT group and 10% in the CTR group (p<0.001). Among HCT recipients, the transplant-related mortality rate was 7.5% at 100 days and 12.5% within 1 year of transplant.

Observational Studies
The evidence has also suggested improvement in symptoms for amyloidosis patients treated with autologous HCT in addition to survival benefits (see Table 1).

Table 1. Observational Studies on Autologous HCT for Primary Amyloidosis

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>N</th>
<th>FU</th>
<th>N at FU</th>
<th>CR Rate, %</th>
<th>OS Rate, %</th>
<th>Median Survival</th>
<th>TRM, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cibeira et al (2011)</td>
<td>421</td>
<td>3 y</td>
<td>340</td>
<td>34</td>
<td>23</td>
<td>57 mo</td>
<td>14</td>
</tr>
<tr>
<td>Madan et al (2012)</td>
<td>187</td>
<td>66 mo</td>
<td>66</td>
<td>20</td>
<td>20</td>
<td>57 mo</td>
<td>16</td>
</tr>
<tr>
<td>Sanchorawala et al (2007)</td>
<td>80</td>
<td>10 y</td>
<td>63</td>
<td>51</td>
<td>51</td>
<td>57 mo</td>
<td>14</td>
</tr>
<tr>
<td>Parmar et al (2014)</td>
<td>80</td>
<td>10 y</td>
<td>HCT=56</td>
<td>51</td>
<td>23</td>
<td>57 mo</td>
<td>14</td>
</tr>
<tr>
<td>1995-2000</td>
<td>140</td>
<td>5 y</td>
<td>55</td>
<td>55</td>
<td>55</td>
<td>55</td>
<td>20</td>
</tr>
<tr>
<td>2001-2006</td>
<td>596</td>
<td>5 y</td>
<td>61</td>
<td>61</td>
<td>61</td>
<td>61</td>
<td>11</td>
</tr>
<tr>
<td>2006-2012</td>
<td>800</td>
<td>5 y</td>
<td>77</td>
<td>77</td>
<td>77</td>
<td>77</td>
<td>5</td>
</tr>
</tbody>
</table>

CR: complete response; CTR: conventional therapies; FU: follow-up; HCT: hematopoietic stem transplantation; OS: overall survival; TRM: treatment-related mortality.

In a 2004 series of 312 amyloidosis patients eligible for transplant, estimated median survival was 4.6 years. Of 181 evaluable patients (alive and followed-up for ≥1 year), 40% achieved complete hematologic response, defined as no evidence of plasma cell dyscrasia at 1 year after transplant with functional improvement in at least 1 affected organ.
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A 2006 registry analysis evaluated 107 amyloidosis patients who received transplants between 1995 and 2001 at 48 centers. For those with no or 1 organ involved at transplant, survival at 1 year was 72%, while for those with 2 or more organs involved, survival at 1 year was 54%. Treatment-related mortality at 30 days was mostly among patients with cardiac and/or multiple organ involvement.

Patients with primary amyloidosis and cardiac involvement were treated in a 2012 series from a single center. Overall, hematologic and cardiac responses were observed in 66% and 41% of patients, respectively.

A 2011 series of 421 consecutive patients treated with HCT at a single referral center compared outcomes for patients with and without a CR. Eighty-one patients died within the first year after HCT and were not evaluable for hematologic and organ response. Of 340 evaluable patients, 43% achieved CR, and 78% of them experienced an organ response. Thus, treatment of selected amyloid light chain amyloidosis patients with autologous HCT resulted in high organ response and longer OS rates, even for those patients who did not achieve CR. These results are compatible with others previously cited.

Several additional retrospective and prospective series were reported in 2012 and 2013 on the use of autologous HCT in patients with primary amyloidosis. Results from these series are consistent with others that have suggested autologous HCT is feasible and beneficial in selected patients with primary amyloidosis.

Long-term survival and outcomes were evaluated in a 2007 series of 80 patients. Among the 32 patients who achieved CR, median survival had not been reached at the time of reporting. In contrast, the median survival for patients who failed to achieve a CR was 50 months, with a 6% estimated probability of survival at 10 years (p<0.001 vs patients with CR).

A 2015 report from the Center for International Blood and Marrow Transplant Research study identified 1536 patients with amyloidosis who had undergone autologous HCT between 1995 and 2012. Early mortality and OS were analyzed for 3 time cohorts: 1995 to 2000, 2001 to 2001, and 2007 to 2012. Over this period, OS rates improved from 55% to 77%, while early mortality rates decreased from 20% to 5%. Multivariate analysis showed that cardiac involvement was associated with high mortality and inferior OS. Higher doses of melphalan were associated with a lowered relapse risk.

Section Summary: Autologous HCT

The evidence related to use of autologous HCT for the treatment of primary amyloidosis includes an RCT, nonrandomized comparative studies, and large case series. The RCT had a number of limitations, and its results are insufficient to determine the effect of the treatment. A retrospective comparison with 10-year follow-up showed a considerable survival advantage for patients treated with HCT. Although retrospective, with evident interstudy patient heterogeneity, this report suggested autologous HCT may yield long-term survival benefits in patients with this disease. Additional case series have shown a CR rate ranging from
34% to 66%, with a clear survival advantage in patients who achieve a CR. Patients who do not achieve a CR may obtain some benefits in organ function. Treatment-related mortality rates from the Center for International Blood and Marrow Transplant Research study have decreased to 5% in recent years, but remain between 11% and 16% in other studies.

**Allogeneic HCT**

Evidence on the use of allogeneic HCT to treat primary amyloidosis is sparse, with no systematic evaluation in a clinical trial. Concerns about the use of allogeneic HCT include high treatment-related mortality (>40%), morbidity secondary to graft-versus-host disease, and the efficacy of a proposed graft-versus-malignancy effect on low-grade plasma cell dyscrasias.

**SUMMARY OF EVIDENCE**

For individuals who have primary amyloidosis who receive autologous HCT, the evidence includes an RCT, nonrandomized comparative studies, and large case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity and mortality. Use of autologous HCT for primary amyloidosis rapidly eradicates the amyloid light chain produced by the clonal plasma cell populations, which is the proximal cause of pathology and subsequent death. This procedure has extended survival rates to a reported 77% at 5 years and 56% at 10 years in patients who respond to treatment. Complete response to treatment has been reported in 34% to 66% of patients, while transplant-related mortality rates have declined to less than 14% in current studies. Therefore, autologous HCT is an important treatment option for patients who are deemed eligible. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have primary amyloidosis who receive allogeneic HCT, the evidence includes case reports. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity and mortality. Evidence on the use of allogeneic HCT is sparse and has shown high treatment-related mortality. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Waldenstrom’s Macroglobulinemia**

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

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HEMATOPOIETIC CELL TRANSPLANTATION FOR WALDENSTRÖM MACROGLOBULINEMIA

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

Autologous HCT
Kyriakou et al (2010) evaluated 158 adults with WM reported to the European Group for Blood and Marrow Transplantation between 1991 and 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 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 2017. Cornell et al (2017) reported retrospectively on 144 adults with WM 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. Sixty-seven patients received myeloablative conditioning (MAC) and 67 received reduced-intensity conditioning (RIC). Over half of patients (n=82 [57%]) had chemosensitive disease. Median follow-up after transplant was 70 months. 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 with patients who had chemoresistant disease. Conditioning intensity (MAC vs RIC) did not impact treatment-related mortality, relapse, or progression-free survival rates. Sixty-five deaths were reported, with the most common causes being graft-versus-host disease (28%) and primary disease (23%).

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Kyriakou et al (2010) retrospectively analyzed data on 86 patients who had allogeneic HCT for WM. Patients underwent 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 chemosensitive 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. The OS rate at 5 years was 62% for MAC and 64% for RIC. Thirty deaths were reported; causes of death included graft-versus-host disease (23%) and primary disease (23%). 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 have reported 5-year OS rates of 52% after allogeneic HCT and 68.5% after autologous HCT. The total number of patients studied was small and there is a lack of published controlled studies.

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.

References


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06/28/2004 Managed Care Advisory Council
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09/05/2007 Medical Director review
09/19/2007 Medical Policy Committee approval. No change in policy statement.
09/09/2008 Medical Director review
09/17/2008 Medical Policy Committee approval. Criteria removed from policy.
04/02/2009 Medical Director review
04/15/2009 Medical Policy Committee approval. Investigational statement for when criteria are not met removed from the policy. No change to coverage eligibility.
09/03/2009 Medical Policy Committee approval
09/16/2009 Medical Policy Implementation Committee approval. Title changed from “High-Dose Chemotherapy with Hematopoietic Stem Cell Support to Treat Primary Amyloidosis or Waldenstrom’s Macroglobulinemia” to Hematopoietic Stem Cell Support to Treat Primary Amyloidosis or Waldenstrom’s Macroglobulinemia “Hematopoietic Stem Cell Transplantation for Primary Amyloidosis or Waldenstrom’s Macroglobulinemia.” No change to coverage eligibility.
09/09/2010 Medical Policy Committee review
09/15/2010 Medical Policy Implementation Committee approval. Changed the language in the coverage section from high-dose chemotherapy with stem cell support to hematopoietic stem-cell transplantation. Coverage eligibility unchanged.
09/01/2011 Medical Policy Committee review

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Hematopoietic Cell Transplantation for Primary Amyloidosis or Waldenstrom’s Macroglobulinemia

Policy #  00138
Original Effective Date: 01/28/2002
Current Effective Date: 11/21/2018

09/14/2011 Medical Policy Implementation Committee approval. “Based on review of available data, the Company may consider autologous hematopoietic stem-cell transplantation as salvage therapy of chemosensitive Waldenstrom macroglobulinemia to be eligible for coverage” was added to the coverage statement. “Autologous hematopoietic stem cell transplantation” was changed to “Allogeneic hematopoietic stem cell transplantation” in the investigational statement for the treatment of Waldenstrom macroglobulinemia.

10/11/2012 Medical Policy Committee review
10/31/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/03/2013 Medical Policy Committee review
10/16/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/06/2014 Medical Policy Committee review
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015 Medical Policy Committee review
11/16/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/03/2016 Medical Policy Committee review
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017 Medical Policy Committee review
11/15/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged. The word Stem removed from title and policy.
11/08/2018 Medical Policy Committee review

Next Scheduled Review Date: 11/2019

Coding
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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38230, 38240, 38241, 38242, 38243</td>
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<tr>
<td>HCPCS</td>
<td>S2140, S2142, S2150</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>C88.0, E85.0-E85.9</td>
</tr>
</tbody>
</table>

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
   1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
   2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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