

8.01.42	Hematopoietic Cell Transplantation for Primary Amyloidosis		
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Policy Statement

Autologous hematopoietic cell transplantation may be considered **medically necessary** to treat primary systemic amyloidosis.

Allogeneic hematopoietic cell transplantation is considered **investigational** to treat primary systemic amyloidosis.

The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered **investigational**.

NOTE: Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

Policy Guidelines

The American Society of Transplantation Consensus Conference on the use of hepatitis C viremic donors in solid organ transplantation concluded that the transplantation of organs from HCV viremic donors into HCV-negative recipients should be conducted only under monitored IRB-approved protocols and studies. (See Supplemental Information).

In 2003, CPT centralized codes describing allogeneic and autologous hematopoietic cell transplantation services to the hematology section (CPT 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 (CPT 38207-38215).

The following CPT codes describe thawing and washing of cryopreserved cells:

- **38208:** Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
- **38209:** Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor

The following CPT codes describe certain cell types being depleted:

- **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

The following CPT codes describes plasma cell concentration:

- **38215:** Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer

Description

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).

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

Rationale

Background

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 exhibits 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 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 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 (e.g., thalidomide, lenalidomide,

pomalidomide) and the proteasome inhibitor, bortezomib. The anti-CD38 monoclonal antibody daratumumab/hyaluronidase-fihj received approval in July 2021 for treatment of newly-diagnosed light chain amyloidosis in combination with bortezomib, cyclophosphamide, and dexamethasone. 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.

Chemotherapy for the treatment of light chain amyloidosis was introduced in 1972 in the form of melphalan and prednisone.¹ This chemotherapy regimen has yielded higher response and longer survival rates than colchicine or prior therapies.^{1,2} Survival after oral melphalan with prednisone (typically 12 to 18 months) is longer than for untreated patients or those given older therapies (10 to 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.^{1,2} However, because of its toxicity, vincristine, doxorubicin, and dexamethasone therapy is usually 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 HCT is being investigated for this disease.

Hematopoietic Cell Transplantation

Hematopoietic cell transplantation 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). These cells 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 (GVHD).

Autologous Hematopoietic Cell Transplantation

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 GVHD.

Allogeneic Hematopoietic Cell Transplantation

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. Human leukocyte antigen 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 (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 the 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 cytotoxic drugs. Furthermore, in any allogeneic HCT, immune suppressant drugs are required to minimize graft rejection and GVHD, 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. These 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 RIC will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the 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 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.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 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. Randomized controlled trials 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.

Autologous Hematopoietic Cell Transplantation

Clinical Context and Therapy Purpose

The purpose of autologous hematopoietic stem cell transplantation (HCT) in patients who have primary amyloidosis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of autologous HCT improve the net health outcome in patients with primary amyloidosis compared with chemotherapy alone?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with primary amyloidosis.

Interventions

The therapy being considered is autologous HCT.

Comparator

The comparator to autologous HCT is chemotherapy alone. 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. Emerging approaches include the use of immunomodulating drugs (e.g., thalidomide, lenalidomide) and the proteasome inhibitor, bortezomib.

Outcomes

The general outcomes of interest are overall survival (OS), disease-specific survival, change in disease status, treatment-related morbidity, and treatment-related mortality. Organ response may include decreases in urinary protein and stabilization of creatinine clearance (kidney); decreases in interventricular septal thickness and improvements in 2 New York Heart Association classes (heart); decreases in abnormal alkaline phosphatase or liver size (liver); and improvements in nerve conduction velocity (nerve).

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Initial results of autologous HCT in uncontrolled patient series were published in 1998.^{3,4} Clinical response rates (50% to 60%) were near twice those reported for conventional therapy, and 2-year survival ranged from 56% to 68%.^{5,6} Kaplan-Meier analysis of a 2004 matched comparison study (63 pairs) showed greater OS for those given autotransplants (71% at 4 years) than for patients who were eligible for transplantation but managed conventionally (41%; $p=.004$).⁶ 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.^{3,7,8}

Systematic Review

Cai et al (2020) performed a literature review and network meta-analysis comparing 6 chemotherapeutic regimens and autologous HCT among 3402 patients with immunoglobulin light-chain amyloidosis.⁹ The analysis included 3 RCTs and 13 observational controlled trials with a sample size ranging from 24 to 796 and mean follow-up of 1 to 5 years. Results revealed that the chemotherapy combination of bortezomib, melphalan, and dexamethasone was ranked first among all evaluated treatments regarding hematologic response and complete response (CR). Autologous HCT was ranked second for hematologic response and fourth for CR. Thalidomide, cyclophosphamide, and dexamethasone induced the highest renal response rate and bortezomib and dexamethasone was possibly the best treatment for a cardiac response per the analysis. Limitations included that hematologic and organ response definitions changed over time, some treatments that were not evaluated in a controlled study were excluded from the analysis, and the majority of included studies were retrospective in nature.

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).¹⁰ 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 2 or more organs affected. Hematopoietic stem cells were obtained from peripheral blood following granulocyte colony-stimulating factor mobilization. According to an intention-to-treat analysis, the hematologic response rate did not differ between groups, with 12 CR (24%) and 14 partial responses (PR, 28%) in the chemotherapy recipients versus 11 CR (22%) and 7 PR (14%) in the HCT group (p=.11). At a median follow-up of 24 months, 20 patients in the chemotherapy group had died versus 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 versus 22.2 months in the autologous HCT group (p=.04). An 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 effective 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 chemotherapy did not receive the planned treatment (5 died before treatment, 1 did not tolerate treatment, 1 received an incorrect treatment).

Nonrandomized Comparative Studies

Table 1 summarizes the available nonrandomized comparative studies. Parmar et al (2014) conducted a retrospective comparative analysis from a single treatment center that provides long-term evidence for improved survival among patients with light chain amyloidosis who underwent autologous HCT compared with conventional therapies.¹¹ Patients underwent autologous HCT (n=80) or conventional therapies (n=65) following induction therapy. Patients were heterogeneous in age, organ involvement, cardiac involvement, renal involvement, and percent of bone marrow blast cells; all were significantly overrepresented in the conventional therapy 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 conventional therapy group (p<.001); median survival at 10 years was 56% in the HCT group and 10% in the conventional therapy group (p<.001). Among HCT recipients, the transplant-related mortality rate was 7.5% at 100 days and 12.5% within 1 year of transplant.

Sharpley et al (2021) published a retrospective case-matched study (N=136) that compared bortezomib and autologous HCT for first-line treatment of light chain amyloidosis.¹² All patients had been diagnosed with amyloidosis within the prior 12 months. Patients were matched using propensity scores that included age, performance status, cardiac and liver markers, and the number of organs involved. At 2 years, OS was similar between groups (hazard ratio, 0.95; 95% confidence interval [CI], 0.41 to 2.20, p=.908). Median progression-free survival (50 vs. 42 months, respectively; p=.058) was also similar between groups.

Table 1. Nonrandomized Comparative Studies on Autologous Hematopoietic Cell Transplantation for Primary Amyloidosis

Study (Year)	N	FU	CR Rate, %	OS Rate, %	Median Survival	TRM, %
Parmar et al (2014) ¹¹	80	10 y		HCT=56 Conventional therapy=10		12.5

Study (Year)	N	FU	CR Rate, %	OS Rate, %	Median Survival	TRM, %
Sharpley et al (2021) ¹²	136	HCT=38.5 mo Bortezomib=26.5 mo	HCT=41.2 Bortezomib=30.2	At 24 mo: HCT=88 Bortezomib=85 mo	HCT=50 mo Bortezomib=42	HCT=8.8 Bortezomib=6

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

Noncomparative Studies

Noncomparative studies have suggested improvement in symptoms for amyloidosis patients treated with autologous HCT in addition to survival benefits (Table 2).

Skinner et al (2004) published a study of 312 amyloidosis patients eligible for transplant, in which the estimated median survival was 4.6 years.¹³ Of 181 evaluable patients (alive and followed for ≥ 1 year), 40% achieved a 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. Vesole et al (2006) published a registry analysis that evaluated 107 amyloidosis patients who received transplants between 1995 and 2001 at 48 centers.¹⁴ 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.

Sanchorawala et al (2007) evaluated long-term survival and outcomes in a study of 80 patients.¹⁵ 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 ($p < .001$ vs. patients with CR).

Cibeira et al (2011) published an observational study of 421 consecutive patients treated with autologous HCT at a single referral center and compared outcomes for patients with and without a CR.¹⁶ 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 light chain amyloidosis patients with autologous HCT resulted in high organ response and longer OS rates, even for patients who did not achieve CR.

Madan et al (2012) published a single-center observational study of 187 patients with primary amyloidosis and cardiac involvement.¹⁷ Overall, hematologic and cardiac responses were observed in 66% and 41% of patients, respectively.

D'Souza et al (2015) published a report from the Center for International Blood and Marrow Transplant Research study, which identified 1536 patients with amyloidosis who had undergone autologous HCT between 1995 and 2012.¹⁸ Early mortality and OS were analyzed for 3 time cohorts: 1995 to 2000, 2001 to 2006, 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.

Sharpley et al (2019) evaluated outcomes in 264 patients with amyloidosis who had undergone an autologous HCT between 1994 and 2018 in the United Kingdom.¹⁹ These patients were analyzed as an entire cohort and then by 4 time cohorts: 1994 to 2000, 2000 to 2006, 2007 to 2012, and 2013 to 2018. The overall median OS after autologous HCT was 87 months (95% CI, 77 to 106 months). A hematologic response was seen in 94.8% of patients and was a strong predictor of time to next treatment ($p < .0001$) and OS ($p = .007$). Treatment-related mortality was 8.7% overall and decreased significantly over time.

Table 2. Noncomparative Studies on Autologous Hematopoietic Cell Transplantation for Primary Amyloidosis

Study (Year)	N	FU	N at FU	CR Rate, %	OS Rate, %	Median Survival	TRM, %
Skinner et al (2004) ¹³ .	312	≥1 y	181	40		4.6 y	13
Vesole et al (2006) ¹⁴ .	107	3 y		66	56		18
Santhorawala et al (2007) ¹⁵ .	80	10 y	63	51	23	57 mo	14
Cibeira et al (2011) ¹⁶ .	421		340	34		6.3 y	11
Madan et al (2012) ¹⁷ .	187					66 mo	16
D'Souza et al (2015) ¹⁸ .							
1995 to 2000	140	5 y			55		20
2001 to 2006	596	5 y			61		11
2006 to 2012	800	5 y			77		5
Sharpley et al (2019) ¹⁹ .		Median FU: 68 mo Range: 2 to 284 mo					
1994 to 2000	64			69.6			18.8
2000 to 2006	44			37.1			13.6
2007 to 2012	65			47.7			6.2
2013 to 2018	91			51.1			1.1

CR: complete response; FU: follow-up; OS: overall survival; TRM: treatment-related mortality.

Several additional retrospective and prospective series on the use of autologous HCT in patients with primary amyloidosis have been published.^{20,21,22,23,24} Results from these series are consistent with others that have suggested that autologous HCT is feasible and beneficial in selected patients with primary amyloidosis.

Section Summary: Autologous Hematopoietic Cell Transplantation

The evidence related to use of autologous HCT for the treatment of primary amyloidosis includes a network meta-analysis, RCT, nonrandomized comparative studies, and large case series. Results from the network meta-analysis comparing 7 treatments for amyloidosis ranked autologous HCT second with regard to hematologic response and fourth regarding CR. 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 69.6%, with a clear survival advantage in patients who receive an HCT. Patients who do not achieve a CR may obtain some benefits in organ function. Treatment-related mortality rates decreased in recent years to 5% in the Center for International Blood and Marrow Transplant Research study and 1.1% in another study from the United Kingdom but remain between 11% and 18% in other studies.

Allogeneic Hematopoietic Cell Transplantation

Clinical Context and Therapy Purpose

The purpose of allogeneic HCT in patients who have primary amyloidosis, is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of allogeneic HCT improve the net health outcome in patients with primary amyloidosis compared with chemotherapy alone?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with primary amyloidosis.

Interventions

The therapy being considered is allogeneic HCT.

Comparator

The comparator to allogeneic HCT is chemotherapy alone. 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. Emerging approaches include the use of immunomodulating drugs (e.g., thalidomide, lenalidomide) and the proteasome inhibitor, bortezomib.

Outcomes

The general outcomes of interest are OS, disease-specific survival, change in disease status, treatment-related morbidity, and treatment-related mortality. Organ response may include decreases in urinary protein and stabilization of creatinine clearance (kidney); decreases in interventricular septal thickness and improvements in 2 New York Heart Association classes (heart); decreases in abnormal alkaline phosphatase or liver size (liver); and improvements in nerve conduction velocity (nerve).

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Wechalekar et al (2008) state in a review that evidence on the use of allogeneic HCT to treat primary amyloidosis consists of isolated case reports, with no systematic evaluation in a clinical trial.²⁵ Concerns about the use of allogeneic HCT include high treatment-related mortality (>40%) and morbidity secondary to GVHD. In addition, the efficacy of a proposed graft-versus-malignancy effect on low-grade plasma cell dyscrasias remains unknown.

Section Summary: Allogeneic Hematopoietic Cell Transplantation

Evidence on the use of allogeneic HCT for the treatment of primary amyloidosis consists of isolated case reports. The reports have shown high treatment-related mortality. Currently, allogeneic HCT for primary amyloidosis has been limited to clinical trials.

Summary of Evidence

For individuals with primary amyloidosis who receive autologous HCT, the evidence includes a network meta-analysis, RCT, nonrandomized comparative studies, and large case series. Relevant outcomes are OS, 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 69.6% of patients, while transplant-related mortality rates have declined significantly in more recent 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 an improvement in the net health outcome.

For individuals with primary amyloidosis who receive allogeneic HCT, the evidence includes case reports. Relevant outcomes are OS, 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 that the technology results in an improvement in the net health outcome.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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 from Blue Cross Blue Shield Association, input was received from 5 academic medical centers, including 3 transplant centers, in 2011. There was support for the policy statements on hematopoietic stem transplantation in the treatment of amyloidosis.

Practice Guidelines and Position Statements

The American Society of Transplantation (2017) convened a consensus conference of experts to address issues related to the transplantation of hepatitis C virus (HCV) viremic solid organs into HCV non-viremic recipients.³⁰ Key findings and recommendations are summarized in Table 3.

Table 3. American Society of Transplantation Consensus Conference - Use of HCV Viremic Donors

	Content Area	Key Point
1	Definition of HCV positive	HCV –viremic reflecting a positive NAT should be adopted
2	Data interpretation	HCV antibody status alone limits interpretation of outcomes of transplantation of HCV “positive” organs
3	Transmission and Treatment	Highest risk for unexpected HCV transmission is associated with organ donation from a person who injected drugs within the eclipse or pre-viremic period
4	OPTN policy	No current policies prevent transplantation of HCV-viremic organs into HCV non-viremic recipients
5	Ethical considerations	Transplantation of HCV-viremic organs into HCV non-viremic recipients should be conducted under site specific IRB approved protocols with multi-step informed consent.

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information’ if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society for Transplantation and Cellular Therapy

In 2020 , the American Society for Transplantation and Cellular Therapy (ASTCT) issued guidelines on indications for hematopoietic cell transplantation (HCT) and immune effector therapy. ²⁶ ASTCT gave the rating of N (not generally recommended; neither evidence nor clinical practice supports the routine use) for the use of allogeneic HCT in the treatment of primary amyloidosis in adults. ASTCT gave a rating of S (standard of care) for the use of autologous HCT in the treatment of primary amyloidosis in adults.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines on systemic light chain amyloidosis (v.1.2022) recommend assessing organ involvement based on amyloidosis consensus criteria in newly diagnosed disease.²⁷ Next, patients should be evaluated for stem cell transplant candidacy. The current guidelines list the following as therapeutic considerations for

management of patients (all category 2A recommendations) along with best supportive care: "high-dose melphalan followed by autologous stem cell transplantation; oral melphalan and dexamethasone; dexamethasone in combination with alpha-interferon; thalidomide plus dexamethasone; lenalidomide and dexamethasone; lenalidomide/cyclophosphamide/dexamethasone; pomalidomide and dexamethasone; bortezomib with or without dexamethasone; bortezomib with melphalan plus dexamethasone; cyclophosphamide, thalidomide, and dexamethasone; and cyclophosphamide, bortezomib, and dexamethasone." Since the optimal therapy remains unknown, the NCCN "strongly encourages treatment in the context of a clinical trial when possible."

International Workshops on Waldenström Macroglobulinaemia

In 2017, the International Workshops on Waldenström Macroglobulinaemia published guidelines on the treatment of several paraproteinaemic neuropathies, one of which is primary, or amyloid light chain, amyloidosis.²⁸ First-line treatment for eligible patients includes an autologous cell transplant preceded by a high-dose regimen combining rituximab with another agent such as a purine analogue, bendamustine, or bortezomib.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

The Centers for Medicare & Medicaid Services has determined that the evidence is adequate to conclude that, when recognized clinical risk factors are employed to select patients for transplantation, high-dose melphalan together with autologous stem cell transplantation can provide a net health benefit for Medicare beneficiaries of any age group with primary amyloidosis (110.23, formerly 110.8.1).²⁹ This technique

"is reasonable and necessary for Medicare beneficiaries of any age with primary amyloid light chain (AL) amyloidosis who meet the following criteria:

- Amyloid deposition in 2 or fewer organs, and,
- Cardiac left ventricular ejection fraction (EF) of greater than 45%."

In addition, autologous HCT "must be used to effect hematopoietic reconstitution following severely myelotoxic doses of chemotherapy ... and/or radiotherapy used to treat various malignancies."

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in November 2021 did not identify any ongoing or unpublished trials that would likely influence this review.

References

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Documentation for Clinical Review

Please provide the following documentation:

- Referring physician history and physical
- Bone marrow transplant consultation report and/or progress notes documenting:
 - Diagnosis (including disease staging) and prognosis
 - Synopsis of alternative treatments performed and results
 - Specific transplant type being requested
- Surgical consultation report and/or progress notes
- Results of completed transplant evaluation including:
 - Clinical history including comorbidities
 - Specific issues identified during the transplant evaluation
 - Consultation reports/letters (when applicable)
 - Correspondence from referring physicians (when applicable)
 - Identification of donor for allogeneic related bone marrow/stem cell transplant (when information available)
- Medical social service/social worker and/or psychiatric (if issues are noted) evaluations including psychosocial assessment or impression of patient's ability to be an adequate candidate for transplant
- Radiology reports including:
 - Chest x-ray (CXR)
 - PET scan, CT scan, and bone survey (as appropriate)
- Cardiology procedures and pulmonary function reports:
 - EKG
 - Echocardiogram
 - Pulmonary function tests (PFTs)
- Biopsy/Pathology reports including:
 - Bone marrow biopsy
 - Lymph node biopsy (as appropriate)

- Laboratory reports

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	38204	Management of recipient hematopoietic progenitor cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
	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, per donor
	38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
	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
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation	
HCPCS	S2140	Cord blood harvesting for transplantation, allogeneic
	S2142	Cord blood-derived stem-cell transplantation, allogeneic
	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 of pre and post-transplant care in the global definition

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
01/07/2011	BCBSA Medical Policy adoption
04/01/2011	Policy revision with position change
05/29/2015	Policy title change from Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis or Waldenström Macroglobulinemia Policy revision without position change
02/01/2017	Policy title change from Hematopoietic Stem Cell Transplantation for Primary Amyloidosis Policy revision without position change
01/01/2018	Coding update
02/01/2018	Policy revision without position change
03/01/2019	Policy revision without position change
11/01/2019	Policy revision without position change
04/01/2020	Annual review. No change to policy statement. Literature review updated.
03/01/2021	Annual review. No change to policy statement. Literature review updated.
04/01/2022	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	AFTER
<p>Hematopoietic Cell Transplantation for Primary Amyloidosis 8.01.42</p> <p>Policy Statement: Autologous hematopoietic cell transplantation may be considered medically necessary to treat primary systemic amyloidosis.</p> <p>Allogeneic hematopoietic cell transplantation is considered investigational to treat primary systemic amyloidosis.</p> <p>The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered investigational.</p>	<p>Hematopoietic Cell Transplantation for Primary Amyloidosis 8.01.42</p> <p>Policy Statement: Autologous hematopoietic cell transplantation may be considered medically necessary to treat primary systemic amyloidosis.</p> <p>Allogeneic hematopoietic cell transplantation is considered investigational to treat primary systemic amyloidosis.</p> <p>The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered investigational.</p>