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Hematopoietic Cell Transplantation for Primary Systemic Amyloidosis

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Coverage

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

Allogeneic hematopoietic cell transplantation **is considered experimental, investigational and/or unproven** to treat primary systemic amyloidosis.

Policy Guidelines

None.

Description

Hematopoietic cell transplantation (HCT) refers to the infusion of hematopoietic stem cells to restore bone marrow function in individuals with cancer 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).

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 of approximately 9 to 14 cases per million person-years with approximately 4000 new cases in the U.S. each year. (1) The typical age at diagnosis is about 50 to 65 years. (2) 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 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. (3) This chemotherapy regimen has yielded higher response and longer survival rates than colchicine or prior therapies. (3, 4) 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. (3, 4) 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 or from a donor. 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 (allo-HCT). Compatibility is established by typing of 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 allo-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 the cytotoxic drugs. Furthermore, in any allo-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 allo-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 policy, the term RIC will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

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

Rationale

Medical policies assess the clinical evidence to determine whether the use of a 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 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.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and 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. 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 individuals who have primary amyloidosis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

Populations

The relevant population of interest is individuals 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 bortezomib-based regimens with use of daratumumab and hyaluronidase-fihj/bortezomib/cyclophosphamide/ dexamethasone as a preferred option.

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 two 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.

Initial results of autologous HCT in uncontrolled patient series were published in 1998. (5, 6) Clinical response rates (50%-60%) were nearly twice those reported for conventional therapy, and 2-year survival ranged from 56% to 68%. (7, 8) A 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=0.004). (8) 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. (5, 9, 10)

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. (11) 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). (12) Randomization was stratified by age (<65 years or ≥65 years) and 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 (ITT) analysis, the hematologic response rate did not differ between groups, with 12 CR (24%) and 14 partial responses (28%) in the chemotherapy recipients versus 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 versus 31 in the autologous HCT group. Among 65 patients who could be evaluated, the ITT median survival for patients assigned to chemotherapy was 56.9 months versus 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 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. (13) Patients underwent autologous HCT (n=80) or conventional therapies (n=65) following induction therapy. Patients were heterogeneous with respect to 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 ($p<0.001$); median survival at 10 years was 56% in the HCT group and 10% in the conventional therapy 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.

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. (14) 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) (13)	80	10 years		HCT=56 Conventional therapy=10		12.5
Sharpley et al. (2021) (14)	136	HCT=38.5 mo Bortezomib=26.5 mo	HCT=41.2 Bortezomib=30.2	At 24 mo: HCT=88 Bortezomib=85	HCT=50 mo Bortezomib=42 mo	HCT=8.8 Bortezomib=6

CR: complete response; FU: follow-up; HCT: hematopoietic cell transplantation; mo: months; N: number; 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. (15) Of 181 evaluable patients (alive and followed 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.

Vesole et al. (2006) published a registry analysis evaluated 107 amyloidosis patients who received transplants between 1995 and 2001 at 48 centers. (16) 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. (17) 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 ($p<0.001$ versus 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. (18) 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 those 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. (19) 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 (CIBMTR) study, which identified 1536 patients with amyloidosis who had undergone autologous HCT between 1995 and 2012. (20) 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. (21) 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 ($p<0.0001$) and OS ($p=0.007$). 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) (15)	312	≥ 1y	181	40		4.6 y	13
Vesole et al. (2006) (16)	107	3 y		66	56		18
Sanchorawala et al. (2007) (17)	80	10 y	63	51	23	57 mo	14
Cibeira et al. (2011) (18)	421		340	34		6.3 y	11
Madan et al. (2012) (19)	187					66 mo	16
D'Souza et al. (2015) (20)							
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) (21)		**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; HCT: hematopoietic cell transplantation; mo: months; N: number; OS: overall survival; TRM: treatment-related mortality; y: year.

Several additional retrospective and prospective series on the use of autologous HCT in patients with primary amyloidosis have been published. (22-26) Results from these series are consistent with others that have suggested 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 were 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 CIBMTR 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 individuals who have primary amyloidosis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

Populations

The relevant population of interest is individuals 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 bortezomib-based regimens with use of daratumumab and hyaluronidase-fihj/bortezomib/cyclophosphamide/ dexamethasone as a preferred option.

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.

Wechalekar et al. (2008) state in a review that evidence on the use of allogeneic HCT (allo-HCT) to treat primary amyloidosis consists of isolated case reports, with no systematic evaluation in a clinical trial. (27) Concerns about the use of allo-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 allo-HCT for the treatment of primary amyloidosis consists of isolated case reports. The reports have shown high treatment-related mortality. Currently, allo-HCT for primary amyloidosis has been limited to clinical trials.

Summary of Evidence

For individuals who have primary amyloidosis who receive autologous hematopoietic cell transplantation (HCT), the evidence includes a network meta-analysis, randomized controlled trials (RCTs), 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 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 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 shows high treatment-related mortality. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American Society for Transplantation and Cellular Therapy

In 2020, the American Society for Transplantation and Cellular Therapy (ASTCT) issued guidelines on indications for HCT and immune effector therapy. (28) 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.1.2025) recommend assessing organ involvement based on amyloidosis consensus criteria in newly diagnosed disease. (1) Next, patients should be evaluated for stem cell transplant candidacy. The current guidelines prefer the regimen of daratumumab and bortezomib/cyclophosphamide/dexamethasone as initial systemic therapy in most patients.

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 currently ongoing/unpublished trial that might influence this policy is listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT06022939	A Phase III, Randomized Study of Daratumumab, Cyclophosphamide, Bortezomib and Dexamethasone (Dara-VCD) Induction Followed by Autologous Stem Cell Transplant or Dara-VCD Consolidation and Daratumumab Maintenance in Patients with Newly Diagnosed AL Amyloidosis	338	Oct 2030

NCT: national clinical trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	36511, 38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38220, 38221, 38222, 38230, 38232, 38240, 38241, 38242, 38243, 81265, 81266, 81267, 81268, 81370, 81371, 81372, 81373, 81374, 81375, 81376, 81377, 81378, 81379, 81380, 81381, 81382, 81383, 86805, 86806, 86807, 86808, 86812, 86813, 86816, 86817, 86821, 86825, 86826, 86828, 86829, 86830, 86831, 86832, 86833, 86834, 86835, 86849, 86950, 86985, 88240, 88241
HCPCS Codes	S2140, S2142, S2150

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
06/15/2025	Document updated with literature review. Coverage unchanged. Reference 29 added; reference 1 and 2 updated.
08/15/2024	Reviewed. No changes.
10/15/2023	Document updated with literature review. Coverage unchanged. Added/updated the following references: 1, 2, 14, and 28.

05/15/2022	Reviewed. No changes.
12/01/2021	Document updated with literature review. Coverage unchanged. Added/updated the following references: 9, 18, and 27.
08/15/2020	Reviewed. No changes.
05/01/2019	Document updated with literature review. Coverage unchanged. References 26-27 added. Title changed from "Hematopoietic Stem-Cell Transplantation for Primary Systemic Amyloidosis".
04/01/2018	Reviewed. No changes.
04/15/2017	Document updated with literature review. Coverage unchanged.
07/01/2016	Reviewed. No changes.
05/01/2015	Document updated with literature review. The policy title changed from Stem-Cell Transplant for Primary Systemic Amyloidosis.
10/15/2013	Document updated with literature review. The following was added: 1) Hematopoietic progenitor cell boost is considered experimental, investigational and unproven; and 2) Any related services for the treatment of primary systemic amyloidosis, such as short tandem repeat (STR) markers, are considered experimental, investigational and unproven. Otherwise, coverage unchanged for other services pertaining to primary systemic amyloidosis. Walderstrom macroglobulinemia removed from this policy and now addressed in new policy SUR703.050. Rationale substantially revised. Title changed from Stem-Cell Transplant for Primary Amyloidosis and Waldenstroms Macroglobulinemia.
04/01/2010	New medical document originating from: SUR703.017, Peripheral/Bone Marrow Stem Cell Transplantation (PSCT/BMT) for Non-Malignancies; SUR703.018, Peripheral/Bone Marrow Stem Cell Transplantation (PSCT/BMT) for Malignancies; SUR703.022, Cord Blood as a Source of Stem Cells (CBSC); SUR703.023, Donor Leukocyte Infusion (DLI); **and** SUR703.024, Tandem/Triple High-Dose Chemoradiotherapy with Stem Cell Support for Malignancies. Stem cell transplant continues to be medically necessary when stated criteria are met. [NOTE: A link to the medical policies with the following titles can be found at the end of the medical policy SUR703.002, Stem-Cell Reinfusion or Transplantation Following Chemotherapy (General Donor and Recipient Information): • Peripheral/Bone Marrow Stem Cell Transplantation (PSCT/BMT) for Non-Malignancies; • Peripheral/Bone Marrow Stem Cell Transplantation (PSCT/BMT) for Malignancies; • Cord Blood as a Source of Stem Cells; • Donor Leukocyte Infusion (DLI); and Tandem/Triple High-Dose Chemoradiotherapy with Stem Cell Support for Malignancies.