# Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 9/1/24**
**(See policy history boxes for previous effective dates)**

# Title: BMT - Hematopoietic Cell Transplantation for Primary Amyloidosis

## Description/Background

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).

### PRIMARY AMYLOIDOSIS

The primary amyloidosis 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 on the basis of 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 (AL) protein is produced at the site of deposition. Primary or AL 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 US each year.(1) The typical age at diagnosis is about 50-65 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 a median survival from diagnosis of approximately 12 months, although outcomes have improved with combination chemotherapy with 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 2021for 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 or almelphalan 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**

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

***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-vs-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 six. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

**Myeloablative (Conventional) Conditioning**
The myeloablative (conventional) practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation. Intense conditioning regimens are limited to individuals whose health status is sufficient to tolerate the administration of cytotoxic agents with total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self-immunologic effector cells. While the slower GVM effect is considered the potentially curative component, it may be overwhelmed by substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host-disease, which increases susceptibility 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 with presumably normal hematopoietic stem cells obtained from the individual before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the individual's disease is in complete remission. Individuals who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

**Reduced-Intensity or Non-myeloablative Conditioning for Allo-HCT**
Reduced-intensity conditioning (RIC), sometimes referred to as non-myeloablative (NMA) conditioning, refers to the pretransplant use of lower doses of cytotoxic drugs with or without less intense regimens of radiotherapy than are used in myeloablative conditioning treatments. Although the definition of RIC/NMA is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC/NMA is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. These RIC/NMA regimens range from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and individual condition. Individuals who undergo RIC/NMA with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism.

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## 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 (CFR) title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

## Medical Policy Statement

*Autologous* hematopoietic cell transplantation is established to treat primary systemic amyloidosis. It is a useful therapeutic option when indicated.

*Allogeneic* hematopoietic cell transplantation is considered experimental/investigational to treat primary systemic amyloidosis. It has not been shown to improve clinical outcomes better than established therapies.

## Inclusionary and Exclusionary Guidelines

**Inclusions**:
*Autologous* hematopoietic cell transplantation to treat primary systemic amyloidosis.

**Exclusions**:
*Allogeneic* hematopoietic cell transplantation to treat primary systemic amyloidosis.

***Check specific group contract or certificate***

## CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

### *Established codes:*

| | | | | | |
|---|---|---|---|---|---|
| 38204* | 38206 | 38207 | 38208* | 38209* | 38210* |
| 38211* | 38212* | 38213* | 38214* | 38215* | 38232 |
| 38241 | S2150* | | | | |

### *Other codes (investigational, not medically necessary, etc.):*

| | | | | | |
|---|---|---|---|---|---|
| 38205* | 38230* | 38240* | 38242* | S2140* | S2142* |

*Allogeneic hematopoietic cell transplantation for the treatment of primary systemic amyloidosis is experimental/investigational.

## POTENTIAL CONTRAINDICATIONS FOR TRANSPLANT:

***Note: Final patient eligibility for transplant is subject to the judgment and discretion of the requesting transplant center.***

The selection process for approved tissue transplants is designed to obtain the best result for each patient. Therefore, relative contraindications to HCT may include, but are not limited to:

- Poor cardiac function: Ejection fraction should be greater than 45% with no overt symptoms of congestive heart failure.

- Poor pulmonary function: Pulmonary function tests must be greater than or equal to 50% of predicted value.
- Poor renal function: Renal creatinine clearance should be greater than 40 ml/min or creatinine must be less than or equal to 2mg/dl.
- Poor liver function: There should be no history of severe chronic liver disease
- Presence of HIV or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus (HTLV-1).

Clinical documentation supplied to the health plan must demonstrate that ***attending staff at the transplant center have considered all contraindications*** as part of their overall evaluation of potential organ transplant recipient ***and have decided to proceed.***

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## Rationale

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, two 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.

The following PICOs were used to select literature to inform this review.

**Clinical Context and Therapy Purpose**
The purpose of HCT, autologous or allogeneic, in individuals who have primary amyloidosis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

**Populations**
The relevant population of interest are individuals with primary amyloidosis.

**Interventions**
The therapy being considered is hematopoietic cell transplantation (HCT), either autologous or allogeneic.

**Comparator**
The comparator to autologous or 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, 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 preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with preference for prospective studies.
- To assess longer 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.

## AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION

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 reportedly ranged from 56% to 68%.(7,8) A Kaplan-Meier analysis of a matched comparison study (63 pairs) showed greater overall survival (OS) for those given auto transplants (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 that involved more than two organ systems or had 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 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) to myeloablative melphalan followed by autologous HCT (n=50).(12) 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 complete responses (CR; 24%) and 14 partial responses (28%) in the chemotherapy recipients versus 11 CR (22%) and seven partial responses (PR 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 intention-to-treat 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 six 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 are 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 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 (CTR).(13) Patients underwent autologous HCT (n=80) or CTR (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 CTR group compared with the HCT group. Median follow-up was three 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.

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) | 80 | 10 y | | HCT=56<br>Conventional therapy=10 | | 12.5 |
| Sharpley et al (2021) | 136 | HCT=38.5 mo<br>Bortezomib=26.5 mo | HCT=41.2<br>Bortezomib=30.2 | At 24 mo:<br>HCT=88<br>Bortezomib=85 | HCT=50 mo<br>Bortezomib=42 mo | HCT=8.8<br>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.(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 one year after transplant with functional improvement in at least 1 affected organ.

Vesole et al (2006) registry analysis that evaluated 107 amyloidosis patients who received transplants between 1995 and 2001 at 48 centers.(16) For those with no or one organ involved at transplant, survival at one year was 72%, while for those with two or more organs involved, survival at one 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<.001 vs. patients with CR).

Ciberira et al (2011) published an observational study of 421 consecutive patients treated with autologous HCT at a single referral center 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 a high organ response and longer OS, 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.(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 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 and2018 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<.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) | 312 | ≥1 y | 181 | 40 | | 4.6 y | 13 |
| Vesole et al (2006) | 107 | 3 y | | 66 | 56 | | 18 |
| Sanchorawala et al (2007) | 80 | 10 y | 63 | 51 | 23 | 57 mo | 14 |
| Cibeira et al (2011) | 421 | | 340 | 34 | | 6.3 y | 11 |
| Madan et al (2012) | 187 | | | | | 66 mo | 16 |
| D'Souza et al (2015) | | | | | | | |
| 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) | | 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.(22-26) 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 HCT*

The evidence related to 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

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.(27) Concerns about the use of allogeneic HCT include high treatment-related mortality (>40%) and morbidity secondary to graft-vs-host disease. In addition, the efficacy of a proposed graft-versus-malignancy effect on low-grade plasma cell dyscrasias remains unknown.

### Section Summary: Allogeneic HCT

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, randomized controlled trials, nonrandomized comparative studies, and large case series. The relevant outcomes are overall survival, disease-specific survival, change in disease status, treatment-related morbidity and treatment-related mortality. Use of autologous HCT for primary amyloidosis rapidly eradicates the amyloidogenic 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 a meaningful improvement in the net health outcome.

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

## Supplemental Information

### CLINICAL INPUT RECEIVED THROUGH 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, Blue Cross Blue Shield Association received input from 5 academic medical centers, including 3 transplant centers, while this policy was under review in 2011. There was support for the policy statements regarding HCT in the treatment of amyloidosis.

### PRACTICE GUIDELINES AND POSITION STATEMENTS

#### American Society for Transplantation and Cellular Therapy

The ASTCT (2020) issued guidelines on the indications for hematopoietic cell transplantation (HCT) and immune effector therapy.(28) ASTCT gave the rating of N (not generally recommended; neither evidence nor clinical practice support the routine use) for the use of allogeneic hematopoietic cell transplantation 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 guidelines on systemic light chain amyloidosis recommend assessing organ involvement based on amyloidosis consensus criteria.(1) Next patients should be evaluated for stem cell transplant candidacy. The current guidelines prefer the regimen of daratumumab and hyaluronidasefihj/bortezomib/cyclophosphamide/dexamethasone as initial systemic therapy in most patients.

### U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable

### ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are 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 |

## Government Regulations National/Local:

National Coverage Determination (NCD) for Stem Cell Transplantation (Formerly 110.8.1) 110.23, Effective Date 1/27/16, Implementation Date 10/3/16

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, formerly110.8.1).(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."

*(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)*

## Related Policies

- Bone Marrow Transplant - Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia
- Bone Marrow Transplant - Hematopoietic Cell Transplantation for Acute Myeloid Leukemia
- Bone Marrow Transplant - Hematopoietic Cell Transplantation for Chronic Myelogenous Leukemia
- Bone Marrow Transplant - Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma - Autologous or Allogeneic
- Bone Marrow Transplant - Hematopoietic Cell Transplantation for CNS Embryonal Tumors and Ependymoma
- Bone Marrow Transplant - Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer
- Bone Marrow Transplant - Hematopoietic Cell Transplantation for Hodgkin Lymphoma
- Bone Marrow Transplant - Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
- Bone Marrow Transplant - Hematopoietic Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome
- Bone Marrow Transplant - Hematopoietic Cell Transplantation for Solid Tumors of Childhood

- Bone Marrow Transplant - Hematopoietic Cell Transplantation for Waldenström's Macroglobulinemia
- Bone Marrow Transplant - Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors
- Bone Marrow Transplant, Allogenic Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias
- Bone Marrow Transplant, Allogenic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms
- Bone Marrow Transplant/Hematopoietic Cell Transplantation for Autoimmune Diseases
- Bone Marrow Transplantation for Breast Cancer
- Bone Marrow Transplantation, Autologous, for Malignant Astrocytomas and Gliomas
- Bone Marrow/Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults

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## References


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*The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through April 2, 2024 the date the research was completed.*

## Joint BCBSM/BCN Medical Policy History

| Policy Effective Date | BCBSM Signature Date | BCN Signature Date | Comments |
|---|---|---|---|
| 5/1/11 | 3/17/11 | 3/3/11 | Joint policy established. Information previously available on the following policies:<br>• Allogeneic BMT-Established<br>• Allogeneic BMT – Investigational<br>• Autologous BMT – Established<br>• Autologous BMT – Investigational |
| 11/1/12 | 8/21/12 | 8/21/12 | Topic split out from former combined policy, "Bone Marrow/Stem-Cell Transplantation for Primary Amyloidosis or Waldenström's Macroglobulinemia."<br><br>No change in policy status.<br><br>NOTE: For ***FEHBP*** only, TANDEM autologous transplants are covered. Tandem auto transplants are not covered for any other group. |
| 11/1/13 | 8/22/13 | 8/27/13 | Routine maintenance. Rationale and references updated. No change in policy status. |
| 7/1/15 | 4/24/15 | 5/8/15 | Routine maintenance.<br>Rationale and references updated. No change in policy status.<br>Added procedure codes S2140, S2142 and S2150. |
| 7/15/16 | 4/19/16 | 4/19/16 | Routine approval |
| 5/1/17 | 2/21/17 | 2/21/17 | Routine maintenance.<br>Rationale and references updated. No change in policy status.<br>Added CPT code 38207. |
| 5/1/18 | 2/20/18 | 2/20/18 | Routine maintenance |
| 5/1/19 | 2/19/19 | | Routine maintenance |
| 9/1/19 | 6/18/19 | | Routine maintenance |
| 9/1/20 | 6/16/20 | | Routine maintenance |
| 9/1/21 | 6/15/21 | | Routine maintenance |

| | | | |
|---|---|---|---|
| 9/1/22 | 6/21/22 | | Routine maintenance |
| 9/1/23 | 6/13/23 | | Routine maintenance (slp)<br>Vendor Managed: N/A |
| 9/1/24 | 6/11/24 | | Routine maintenance (slp)<br>Vendor Managed: N/A |

Next Review Date: 2nd Qtr, 2025

# BLUE CARE NETWORK BENEFIT COVERAGE
# POLICY: BMT-HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR PRIMARY AMYLOIDOSIS

## I. Coverage Determination:

| | |
|---|---|
| **Commercial HMO (includes Self-Funded groups unless otherwise specified)** | *Single* autologous cell transplant - covered; criteria apply. *Tandem* autologous cell transplants are not covered for the diagnosis of primary amyloidosis.<br><br>**Note: for FEHBP certificates only: Tandem autologous cell transplants are covered for the treatment of amyloidosis.**<br><br>Allogeneic Cell Transplant – not covered for the diagnosis of primary amyloidosis. |
| **BCNA (Medicare Advantage)** | Refer to Medicare information under the Government Regulations section of this policy. |
| **BCN65 (Medicare Complementary)** | Coinsurance covered if primary Medicare covers the service. |

## II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage