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Medical Policy Manual

Topic: Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis or Waldenstrom Macroglobulinemia

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Hematopoietic Stem-Cell Transplantation

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

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA A, B, and DR loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

Conventional Preparative Conditioning for HSCT

The conventional ("classical") practice of allogeneic HSCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that develops after engraftment of allogeneic stem cells within the patient's bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HSCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HSCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient prior to undergoing bone marrow ablation. As a consequence, autologous HSCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

Reduced-Intensity Conditioning for Allogeneic HSCT

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden, but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HSCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For the purposes of this policy, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

Primary Systemic Amyloidosis

The primary amyloidoses comprise a group of diseases with an underlying clonal plasma cell dyscrasia. They are characterized by the extracellular deposition of pathologic, insoluble protein fibrils with a beta-pleated sheet configuration that exhibit a pathognomonic red-green birefringence when stained with Congo red dye and examined under polarized light. These diseases are classified on the basis of the type of amyloidogenic protein involved, as well as 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 protein is produced at the site of deposition. Also called, light-chain amyloidosis (AL) primary systemic amyloidosis is the most common type of systemic amyloidosis. The

amyloidogenic protein in primary systemic amyloidosis is an immunoglobulin (Ig) light chain or light-chain fragment that is produced by a clonal population of plasma cells in the bone marrow. Deposition of primary systemic amyloidogenic proteins causes organ dysfunction, most frequently in the kidneys, heart, and liver, although the central nervous system and brain may be affected.

Historically, this disease has had a poor prognosis, with a median survival from diagnosis of about 12 months, although outcomes have improved with the advent of combination chemotherapy with alkylating agents and autologous HSCT. Emerging approaches include the use of immunomodulating drugs such as thalidomide or lenalidomide, and the proteasome inhibitor bortezomib. Regardless of the approach chosen, treatment of primary systemic amyloidosis is aimed 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.

Waldenstrom Macroglobulinemia

Waldenstrom macroglobulinemia (WM) is a rare B-cell malignancy. Median survival of WM ranges from 5 to 10 years, with age, hemoglobin concentration, serum albumin level, and beta-2 microglobulin level as predictors of outcome. The Revised European American Lymphoma (REAL) and World Health Organization (WHO) classification and a consensus group formed at the Second International Workshop on WM recognize WM primarily as a lymphoplasmacytic lymphoma (LPL) with an associated immunoglobulin M (IgM) monoclonal gammopathy.[1] The definition also requires the presence of a characteristic pattern of bone marrow infiltration with small lymphocytes demonstrating plasmacytic differentiation with variable cell surface antigen expression. The Second International Workshop indicated no minimum serum concentration of IgM is necessary for a diagnosis of WM.

Treatment of WM is indicated only in symptomatic patients, and should not be initiated solely on the basis of serum IgM concentration.[2]

MEDICAL POLICY CRITERIA

I. Autologous HSCT

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

B. Autologous hematopoietic stem-cell transplantation is may be considered **medically necessary** as salvage therapy for chemosensitive Waldenstrom macroglobulinemia.

II. Allogeneic HSCT

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

B. Allogeneic hematopoietic stem-cell transplantation is considered **investigational** to treat Waldenstrom macroglobulinemia.

SCIENTIFIC EVIDENCE

The principal outcomes associated with treatment of primary systemic amyloidosis or Waldenstrom macroglobulinemia are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Patient quality of life may be another primary outcome, particularly among patients living with refractory disease. Ideally, the impact of hematopoietic stem cell transplantation on the treatment of these conditions is best understood in well-designed randomized controlled trials (RCTs) that compare this therapy to standard medical treatment, such as conventional standard-dose chemotherapy. Further, for treatment of malignant cancers, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits associated with treatment to understand the net treatment effect.

Primary Systemic Amyloidosis

Several clinical trials, including a randomized controlled trial, and several non-comparative case series and registry reports have been reported on the use of autologous hematopoietic stem-cell transplantation (HSCT) in patients with primary systemic amyloidosis. To date, no evidence from clinical trials has been identified on the use of allogeneic HSCT for treatment of primary systemic amyloidosis.

Randomized Controlled Trial (RCT)

One randomized multicenter trial involving 8 centers from the Myelome Autogreffe (MAG) and Intergroupe Francophone du Myelome (IFM) Intergroup compared conventional chemotherapy with melphalan plus dexamethasone with myeloablative melphalan followed by autologous HSCT in patients with AL amyloidosis.[3] Patients between 18 and 70 years of age with a histological diagnosis of AL amyloidosis and either a complete hematologic response characterization of amyloid deposits or evidence of a monoclonal Ig protein in the serum or urine or a monoclonal staining pattern of bone marrow plasma cells and history of no more than two courses of any chemotherapy regimen. They were stratified according to age (younger than 65 years or 65 years or older) and according to the affected organ system (cardiac, renal, neurological, or other) and randomly allocated. Patients in the melphalan plus dexamethasone group (n=50) received monthly courses of dose-adjusted (according to cytopenic status) oral melphalan, 10 mg/m2 of body-surface area, on days 1 to 4 plus oral dexamethasone, 40 mg/day on days 1 to 4, for up to 18 courses if no severe adverse events occurred. In the autologous HSCT patients (n=50), hematopoietic stem cells were obtained from peripheral blood with granulocyte colony-stimulating factor mobilization. Melphalan was administered intravenously on day 0, and stem cells were infused on day 2, with the dose reduced from 200 mg/m2 to 140 mg/m2 for patients aged 65 years or older and for those with an LVEF <30%, a calculated creatinine clearance <30 mL/min, or severe liver disease. According to intention-to-treat analysis, the hematologic response rate did not differ between groups, with 12 CR (24%) and 14 PR (28%) in the melphalan-dexamethasone recipients versus 11 CR (22%) and 7 PR (14%) in the autologous HSCT group (p=0.11). At publication of the study, the median follow-up for the entire cohort was 24 months, and for survivors it was 36 months; 20 patients in the melphalan-dexamethasone group had died versus 31 in the autologous HSCT group. Among 65 patients who could be evaluated, the intention-to-treat median survival for patients assigned to melphalan plus dexamethasone was 56.9 months, versus 22.2 months in the autologous HSCT group (p=0.04). Survival rates and duration were significantly better in responders (CR plus PR) compared to NR (p<.0001). Analysis of patients who survived for at least 6 months and who received their assigned treatment, showed no significant difference in survival rates in patients assigned to melphalan plus

dexamethasone compared to autologous HSCT, with neither group reaching median survival after 80 months (p=0.38).

This randomized trial suggests that autologous HSCT may be no more efficacious than conventional chemotherapy in prolonging survival among patients with AL amyloidosis. However, the results are limited by the size of the study, a lack of assessor blinding or allocation concealment, and a large attrition post-randomization. Thus, among 50 patients assigned to autologous HSCT, 13 (26%) did not receive the planned treatment (1 declined, 2 had insufficient stem-cell harvest, 10 died before treatment) whereas 7 of 50 (14%) assigned to melphalan plus dexamethasone did not receive planned treatment (5 died before treatment, 1 did not tolerate treatment, 1 received incorrect treatment). Therefore, even though this was a randomized trial, the results are not sufficient to change the policy statement given the body of evidence available from other, albeit nonrandomized, studies.

Non-Randomized Studies/Registry Reports

Several retrospective and prospective series have been reported on the use of autologous HSCT in patients with AL. Results from these series are consistent with others that suggest autologous HSCT is feasible and beneficial in selected patients with AL.[4-23]

Available evidence is sufficient to demonstrate a treatment benefit associated with autologous HSCT in patients with primary amyloidosis. Data on the use of allogeneic HSCT to treat AL amyloidosis are sparse, with no systematic evaluation in a clinical trial.[24] Until clinical trials reporting the use of allogeneic HSCT are reported in the scientific literature, the safety and effectiveness of this treatment in primary amyloidosis will remain unknown.

Waldenstrom Macroglobulinemia

The evidence supporting the use of autologous or allogeneic hematopoietic stem-cell transplantation (HCST) in patients with Waldenstrom macroglobulinemia (WM) consists of non-randomized trials, several of them retrospective.

Non-Randomized Studies/Registry Reports

- A retrospective Center for International Blood and Marrow Transplant Research (CIBMTR) registry analysis of SCT (autologous, n=10, allogeneic, n=26) for WM reported 3-year overall survival rates of 46% (95% CI: 27–65%) for allogeneic HSCT recipients and 70% (95% CI: 40–93%) for autologous HSCT patients.[25] Although the CIBMTR results appear favorable, it should be noted that patients in this report were heavily pretreated, highly heterogeneous in terms of disease characteristics and risk factors, and received a variety of conditioning regimens, including myeloablative and RIC, between 1986 and 2002.

- Kyriakou et al. reported on 158 adult patients with Waldenstrom macroglobulinemia reported to the European Group for Blood and Marrow Transplantation (EBMT) between January 1991 and December 2005.[26] Median time from diagnosis to autologous HSCT was 1.7 years (range, 0.3 to 20.3 years), 32% of the patients had experienced treatment failure with at least three 3 of therapy, and 93% had sensitive disease at the time of SCT. Median follow-up for surviving patients was 4.2 years (range: 0.5 to 14.8 years). Nonrelapse mortality was 3.8% at 1 year. The estimated 5-year relapse rate was 52.1%. Progression-free survival (PFS) and OS were 39.7% and 68.5%, respectively, at 5 years and were significantly influenced by number of lines of therapy and

chemorefractoriness at HSCT. The authors conclude that autologous HSCT is a feasible procedure in young patients with advanced Waldenstrom macroglobulinemia but that it should not be offered to patients with chemoresistant disease and to those who received more than 3 lines of therapy.

- Kyriakou and colleagues also reported on a retrospective analysis of a smaller group of patients who had allogeneic HSCT for Waldenstrom macroglobulinemia.[27] A total of 86 patients received allogeneic HSCT by using either myeloablative conditioning (MAC; n=37) or reduced-intensity conditioning (RIC; n=49) regimens. The median age was 49 years (range: 23 to 64 years); 47 patients had received 3 or more previous lines of therapy, and 8 patients had experienced failure on a prior autologous HSCT. A total of 59 patients (68.6%) had chemotherapy-sensitive disease at the time of allogeneic SCT. Median follow-up of the surviving patients was 50 months. The overall response rate was 75.6%. The relapse rates at 3 years were 11% for MAC and 25% for RIC. Overall survival at 5 years was 62% for MAC and 64% for RIC, respectively. The occurrence of chronic graft-versus-host (GVH) disease was associated with a lower relapse rate. The authors concluded that allogeneic SCT can induce durable remissions in a selected population of young and heavily pretreated patients who have Waldenstrom macroglobulinemia.

As in primary systemic amyloidosis, available data on the use of autologous HSCT for Waldenstrom macroglobulinemia are sufficient (because of rarity of the disease) to indicate a potential treatment benefit in patients with this rare type of B cell malignancy who have failed other treatment options. Available evidence is not sufficient to indicate whether patients treated with allogeneic HSCT experience a similar treatment benefit.

Clinical Practice Guidelines

AL Amyloidosis

The 2014 National Comprehensive Cancer Network (NCCN) guidelines discuss optional treatments, including autologous HSCT, as primary therapy for systemic amyloidosis; however, they caution that the optimal therapy is not established and that such treatment would best be performed in a clinical trial.[29]

Waldenstrom Macroglobulinemia

Two clinical practice guidelines were identified which recommend allogeneic HSCT only within the research setting for Waldenstrom macroglobulinemia patients:

- The 2013 National Comprehensive Cancer Network (NCCN) guidelines indicate that selected cases of Waldenstrom's macroglobulinemia may be treated with autologous or allogeneic HSCT, but the latter only in a clinical trial.[30]
- A consensus panel from the Fifth International Workshop on Waldenstrom's Macroglobulinemia recommended that autologous HSCT may be considered for selected patients with refractory or relapsing disease, but allogeneic transplants should be used only in the context of a clinical trial.[31]

Summary

Primary Systemic Amyloidosis

Autologous Hematopoietic Stem-Cell Transplantation

Due to the rarity of this disease, and the poor prognosis associated with diagnosis, evidence from available clinical trials is sufficient to demonstrate a treatment benefit of autologous HSCT in patients with primary systemic amyloidosis. Therefore, use of this procedure may be considered medically necessary.

Allogeneic Hematopoietic Stem-Cell Transplantation

Concerns about the use of allogeneic SCT include high treatment-related mortality, morbidity secondary to graft-versus-host disease, and questions about the efficacy of a proposed graft-versus-malignancy effect on low-grade plasma cell dyscrasias. Current data on the use of allogeneic SCT to treat primary systemic amyloidosis are sparse and do not allow for conclusions about the net benefit of this treatment after accounting for risk of such concerns. Therefore, allogeneic HSCT is considered investigational in patients with primary systemic amyloidosis.

Waldenstrom Macroglobulinemia

Autologous Hematopoietic Stem-Cell Transplantation

Given the rarity of this condition, available evidence on the use of autologous HSCT for treatment of Waldenstrom macroglobulinemia (WM) is sufficient to demonstrate a treatment benefit among patients who have failed first-line medical therapies. Current NCCN guidelines concur with the appraisal of the evidence and recommend that this treatment be considered only among patients who have failed previous treatment. Therefore, the use of autologous HSCT as salvage treatment for WM is considered medically necessary.

However, available scientific evidence is not sufficient to identify the treatment effect of autologous HSCT compared to first-line treatments of WM. Use of this procedure as a primary treatment of WM is considered investigational. In order to establish the relative treatment benefit of autologous HSCT as a first-line treatment for WM, prospective clinical trials comparing outcomes of patients treated with autologous HSCT versus standard first-line treatments are needed.

Allogeneic Hematopoietic Stem-Cell Transplantation

There is insufficient evidence to weigh the risk of adverse effects against any potential treatment benefit from allogeneic HSCT as a treatment for Waldenstrom macroglobulinemia (WM). Current NCCN guidelines do not recommend the use of this type of transplantation outside the research setting. Therefore use of allogeneic HSCT for treatment of WM is considered investigational. Additional trials are needed to establish the net treatment benefit associated with allogeneic HSCT for WM.

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CROSS REFERENCES

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Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16

Hematopoietic Stem-Cell Transplantation for Non-Hodgkin Lymphomas, Transplant, Policy No. 45.23

Hematopoietic Stem Cell Transplantation for Hodgkin Lymphoma, Transplant, Policy No. 45.30

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

CODES	NUMBER	DESCRIPTION
	38241	;autologous transplantation
	38242	Allogeneic lymphocyte infusions
	38243	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor, HPC boost
HCPCS	J9000–J9999	Chemotherapy drugs code range
	Q0083–Q0085	Chemotherapy administration code range
	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)