



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Stem-Cell Transplantation for Hodgkin Disease

Effective Date 10/15/2010
Next Review Date.....10/15/2011
Coverage Policy Number0188

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Coverage Policy

CIGNA covers autologous hematopoietic stem-cell transplantation (HSCT) following high-dose chemotherapy as medically necessary for the treatment of refractory, primary progressive, or recurrent Hodgkin disease.

CIGNA covers myeloablative allogeneic HSCT from a human leukocyte antigen (HLA)-matched donor (at least five of six HLA-match) as medically necessary for the treatment of refractory, primary progressive, or recurrent Hodgkin disease when the individual is not a candidate for autologous HSCT.

CIGNA covers nonmyeloablative allogeneic HSCT from a human leukocyte antigen (HLA)-matched donor (at least five of six HLA-match) as medically necessary for the treatment of Hodgkin disease that is relapsed or refractory after prior HSCT.

CIGNA does not cover any of the following procedures for the treatment of Hodgkin disease because they are considered experimental, investigational or unproven (this list may not be all-inclusive):

- nonmyeloablative allogeneic HSCT for any other indication
- tandem hematopoietic stem-cell transplantation

General Background

Hodgkin disease (HD), also called Hodgkin lymphoma, is an uncommon malignancy involving the lymph nodes and lymphatic system. HD is divided into two main classes (i.e., classical, nodular lymphocyte-predominant) according to specific tumor-cell characteristics. Additionally, each stage of HD can be further subclassified into two categories, A and B. The presence of category B or constitutional symptoms (i.e., unexplained weight loss of more than 10% of body weight in the six months before diagnosis, unexplained fever with temperatures above 38° C (100.4°F), drenching night sweats), is considered an adverse prognostic factor (Horning, 2008; National Cancer Institute [NCI], 2010a, NCI, 2010b). Other factors associated with adverse prognosis include extranodal sites of disease, complete response <1 year duration, and primary refractory disease. Type/intensity of treatment is based, in part, on the presence of prognostic factors. Adults who do not respond to induction chemotherapy have less than a 10% survival rate at eight years. Stem-cell transplantation has been proposed for the treatment of individuals with refractory, primary progressive, or recurrent HD.

Stem-Cell Transplantation

Hematopoietic stem-cell transplantation (HSCT) refers to the transplantation of hematopoietic stem cells (HSC) from a donor into a recipient. HSCs are immature cells that can develop into any of the three types of blood cells (i.e., red cells, white cells or platelets). HSCT can be either autologous (i.e., using the patient's own stem cells) or allogeneic (i.e., using stem cells from a donor).

Autologous HSCT

Adult HD: High-dose chemotherapy and autologous HSCT has been the most successful treatment approach for patients younger than age 60 years with refractory, primary progressive, or relapsed disease, although improvement in overall survival (OS) has not been shown in randomized studies (Horning, 2008). The rationale for this therapy is the assumption of a steep dose-response. High-dose chemotherapy is frequently used in patients with first or higher relapses of HD, while there are limited data concerning its use in advanced-stage HD (Diehl, 2008).

In two randomized trials comparing aggressive conventional chemotherapy with high-dose chemotherapy and autologous HSCT for refractory and relapsed HD (Schmitz, 2002; Linch, 1993), an improvement in freedom from treatment failure was seen, with event-free (EFS) and disease-free survival (DFS) rates at three-and five-years of 17-48% for the transplantation arm. No differences in OS were observed. Improved response and DFS rates have also been reported in uncontrolled case reviews and retrospective registry analyses.

When relapse occurs after effective primary chemotherapy, there is only a 20% chance that additional standard-dose chemotherapy will result in long-term, disease-free survival (Diehl, 2003). Adults who relapse after initial combination chemotherapy usually undergo reinduction followed by high-dose chemotherapy and autologous bone marrow or peripheral stem cell or allogeneic bone marrow rescue. Clinical trials have demonstrated three- to four-year DFS rates of 27% to 48%; no differences were noted in OS, although patients who are responsive to reinduction chemotherapy may have a better prognosis (NCI, 2010a).

A recent case series report by Sirohi et al. (2008) involving data gathered on 195 consecutive patients with relapsed/refractory HD who received high dose chemotherapy and autologous HSCT demonstrated a complete response in 61% of patients. Median OS was nine years, and median progression-free survival (PFS) was 2.9 years. Five-year OS and PFS rates were 55% and 44%; ten-year OS and PFS rates were 49.4% and 37%.

Childhood HD: Therapy for children with low-stage disease that are initially treated with dose-intensive treatment usually includes induction chemotherapy, and high-dose chemotherapy with hematopoietic stem cell transplant therapy for relapse or progression (HSCT) (NCI, 2009b). Following autologous HSCT, the projected survival rate is 45% to 70% and progression-free survival is 30% to 70% in selected individuals with primary progressive or relapsed disease (Diehl, 2008).

Outcomes for children with primary refractory HD are poor even with HSCT (NCI, 2010b). Akhtar et al. (2008) reported results of a retrospective cohort analysis involving 66 patients with relapsed/refractory HD who received high-dose chemoradiotherapy and autologous HSCT. Median EFS at 22.8 months was 36% and median OS was not reached at the time of report publication.

Despite data demonstrating a lack of improved overall survival outcomes with the use of high-dose chemotherapy and stem-cell transplantation compared with aggressive conventional therapy, autologous HSCT is considered an appropriate therapy for selected individuals with Hodgkin disease (HD).

Allogeneic HSCT

Myeloablative conditioning: Although autologous hematopoietic stem-cell transplantation (HSCT) results in overall better outcomes compared with allogeneic HSCT, many adults and children may be ineligible for autologous HSCT because of gross bone marrow contamination with diseased cells or the inability to mobilize sufficient hematopoietic stem-cells. Additionally, the use of a matched sibling marrow donor results in a lower relapse rate compared with autologous HSCT (NCI, 2010a; Akpek, 2001; Nachbaur, 2001). In two retrospective studies the probability of relapse with allogeneic HSCT was 30%–34%, compared with 38%–51% with autologous HSCT (Akpek, 2001; Nachbaur, 2001). A limitation of allogeneic HSCT is a relatively high rate of transplant-related mortality (TRM), usually associated with graft-versus-host-disease (GVHD) and infection. In patients with elevated serum lactic dehydrogenase and bone marrow involvement at the time of transplantation, allogeneic was superior to autologous HSCT and resulted in better outcome due to a lower relapse incidence, suggesting the existence of a graft-versus-lymphoma effect. For selected individuals myeloablative allogeneic HSCT is an accepted treatment option.

Nonmyeloablative conditioning: Use of nonmyeloablative allogeneic HSCT has been proposed for the treatment of selected individuals with HD. There are outstanding questions regarding the most effective conditioning regimen to use and the extent to which the graft-versus-lymphoma effect eradicates the tumor.

A retrospective analysis was performed by Sureda et al., (2008), comparing the clinical outcomes of 168 patients with relapsed HD that were registered in the European Group for Blood and Marrow Transplant database. Patients were treated with an allogeneic HSCT using either reduced-intensity (RIC) (n=89) or myeloablative conditioning (n=79). Non-relapse mortality was significantly reduced in the RIC group compared with the myeloablative group. Five-year overall survival (OS) rates for the RIC and myeloablative groups were 28% and 22%, respectively. Fifty-seven percent of patients in the RIC group and 30.4% of patients in the myeloablative group experienced relapse after a median time of six months; risk of relapse was higher in the RIC group on univariate analysis but not on multivariate analysis. The development of graft-versus-host disease (GVHD) significantly decreased the incidence of relapse.

Anderlini et al., (2007) reported a retrospective analysis of the outcomes for 58 patients with relapsed and refractory HD who underwent reduced-intensity conditioning followed by allogeneic HSCT. Forty-eight patients (83%) had previously undergone autologous HSCT. Projected two-year OS and progression-free survival (PFS) rates were 64% and 32%, respectively. The use of fludarabine-melphalan was associated with a reduction in TRM. In other case studies and registry data analysis, use of nonmyeloablative allogeneic HSCT has resulted in two- to four-year OS and PFS survival rates of 37%–73% and 18%–39%, respectively (Devetten, 2009; Todisco, 2007; Alvarez, 2006; Peggs, 2005; Burroughs, 2004).

Overall, there appears to be lower TRM, and improved PFS with the use of nonmyeloablative allogeneic HSCT in this subset of patients. Although comparative data are limited, this therapy is an acceptable treatment option for patients with relapsed or refractory HD following previous HSCT.

Tandem Transplant: Tandem HSCT involves performing consecutive HSCTs in an effort to consolidate or intensify the effect of chemotherapy. The goal is to induce a longer remission in a patient with refractory or recurrent Hodgkin disease. Although there are some published peer-reviewed feasibility studies for this indication, studies are limited by small populations, the inability to identify prognostic factors, short follow-up, and the lack of randomized clinical trials. The role of tandem HSCT has not yet been established.

Contraindications

Many factors affect the outcome of a tissue transplant. The individual's overall health, age and disease stage are extremely important considerations in evaluating patients. The presence of any significant comorbid conditions which would significantly compromise clinical care and chances of survival is a contraindication to transplant. Relative contraindications to HSCT include, but are not limited to:

- poor cardiac function (ejection fraction less than 45%)

- poor liver function (bilirubin greater than 2.0 mg/dL and transaminases greater than two times normal), unless related to disease
- poor renal function (creatinine clearance less than 50 ml/min)
- poor pulmonary function (diffusion capacity less than 60% of predicted)
- presence of human immunodeficiency virus or of an active form of hepatitis B, hepatitis C or human T cell lymphotropic virus (HTLV-1)
- Karnofsky rating less than 60% and/or Eastern Cooperative Oncology Group (ECOG) performance status greater than two
- advanced age

Professional Societies/Organizations

National Marrow Donor Program (NMDP)/American Society for Blood and Marrow Transplantation

(ASBMT) (2008): For Hodgkin lymphoma, HSCT referral guidelines recommend referral for individuals who have no initial complete response to chemotherapy and for those in first or subsequent relapse.

National Cancer Institute (NCI) (2010a; 2010b): Regarding advanced, unfavorable HD, the NCI notes “Controversy exists about whether the optimal strategy should involve early dose intensification, with subsequent risks of increased late toxic effects (such as leukemia) or whether ABVD should be employed and patients who relapse be salvaged with high-dose treatment and autografting.”

Recurrent adult HD: “Patients who relapse after initial combination chemotherapy usually undergo reinduction with the same or another chemotherapy regimen followed by high-dose chemotherapy and autologous bone marrow or peripheral stem cell or allogeneic bone marrow rescue, which may result in a three- to four-year DFS rate of 27% to 48%. Patients who are responsive to reinduction chemotherapy may have a better prognosis.”

“High-dose chemotherapy and autologous bone marrow or peripheral stem cell or allogeneic bone marrow rescue are under clinical evaluation for patients who do not respond to induction chemotherapy.”

Regarding the use of autologous or allogeneic hematopoietic stem-cell transplantation (HSCT) for children and adolescents with primary progressive/recurrent Hodgkin lymphoma, the NCI (2008) notes in patients who are initially treated for low-stage disease without dose-intensive therapy, the salvage rates without hematopoietic stem cell transplant are very high. For all other patients, treatment of relapse/progression includes induction chemotherapy, and high-dose chemotherapy with HSCT. Overall outcome is better following the use of autologous versus allogeneic stem cells because of the increased mortality associated with allogeneic transplant. For patients who fail following autologous HSCT or for patients who cannot mobilize sufficient numbers of autologous stem cells, allogeneic HSCT has been used with encouraging results.

National Comprehensive Cancer Network Guidelines™ (NCCN Guidelines™) (2010): Regarding treatment of progressive disease or relapse the NCCN Practice Guidelines in Oncology for Hodgkin Disease/Lymphoma (HD/HL) notes “High-dose therapy/autologous stem-cell rescue (HDT/ASCR) is the best option for patients with Hodgkin lymphoma that is incurable with primary treatment, although it does not improve overall survival.”

Italian Society of Hematology, Italian of Experimental Hematology, and Italian Group for Bone marrow Transplantation (2008): Guidelines published by Brusomolino et al. (2008) on behalf of these three groups note that individuals younger than age 60–65 with relapsed or refractory HD should receive high-dose chemotherapy and autologous hemopoietic stem cells transplant. An allogeneic HSCT is recommended in patients with early relapses or refractory to one–two lines of chemotherapy, who fail to collect a suitable number of autologous stem-cells. A reduced-intensity conditioning is recommended.

Summary

Although data are not robust, autologous or allogeneic hematopoietic stem-cell transplantation (HSCT) are considered acceptable treatment options for selected individuals with refractory, primary progressive, or recurrent Hodgkin disease (HD). For individuals with relapsed or refractory Hodgkin disease after prior HSCT, the use of nonmyeloablative conditioning is a reasonable option. The role of tandem HSCT has not yet been established.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT®* Codes	Description
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38230	Bone marrow harvesting for transplantation
38240	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic
38241	Bone marrow or blood-derived peripheral stem cell transplantation; autologous
38242	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions

HCPCS Codes	Description
S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood-derived stem-cell transplantation, allogeneic
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage; marrow ablative therapy; drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days or pre-and post-transplant care in the global definition

ICD-9-CM Diagnosis Codes	Description
201.00- 201.08	Hodgkin's disease
201.10- 201.18	Hodgkin's granuloma
201.20- 201.28	Hodgkin's sarcoma
201.40- 201.48	Hodgkin's disease, lymphocytic-histiocytic predominance
201.50-	Hodgkin's disease, nodular sclerosis

201.58	
201.60- 201.68	Hodgkin's disease, mixed cellularity
201.70- 201.78	Hodgkin's disease, lymphocytic depletion
201.90- 201.98	Hodgkin's disease, unspecified

***Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.**

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	9/15/2008	0188	Stem-Cell Transplant for Hodgkin Disease
Great-West Healthcare	6/21/2007	05.289.02	Bone Marrow Transplantation (BMT) for Hodgkin's Disease

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