Stem-Cell Transplantation for Hodgkin Disease

Table of Contents

Coverage Policy .................................................. 1
Overview ............................................................ 1
General Background ........................................... 2
Coding/Billing Information ................................. 2
References ......................................................... 7

Related Coverage Resources

<table>
<thead>
<tr>
<th>Resource</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor Lymphocyte Infusion</td>
</tr>
<tr>
<td>Oncology Medications</td>
</tr>
<tr>
<td>Transplantation Donor Charges</td>
</tr>
<tr>
<td>Umbilical Cord Blood Banking</td>
</tr>
</tbody>
</table>

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Coverage Policy

Autologous hematopoietic stem-cell transplantation (HSCT) following high-dose chemotherapy is considered medically necessary for the treatment of refractory, primary progressive or recurrent Hodgkin disease.

Myeloablative allogeneic HSCT from an appropriately-matched human leukocyte antigen (HLA) donor is considered medically necessary for the treatment of refractory, primary progressive, or recurrent Hodgkin disease when the individual is not a candidate for autologous HSCT.

Nonmyeloablative allogeneic HSCT from an appropriately-matched HLA donor is considered medically necessary for the treatment of Hodgkin disease that is relapsed or refractory after prior HSCT.

Each of the following procedures for the treatment of Hodgkin disease is considered experimental, investigational or unproven:

- nonmyeloablative allogeneic HSCT for any other indication
- tandem HSCT

Overview

This Coverage Policy addresses stem cell transplantation for the treatment of Hodgkin disease.
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 is subdivided into categories, A and B. Type/intensity of treatment is based, in part, on the presence of prognostic factors.

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. Other factors associated with adverse prognosis include mediastinal bulk, more than three nodal sites of disease, >45 years of age, male gender, stage IV disease, albumin level <4g/dL, hemoglobin <10.5g/dL, lymphocytosis, lymphocytopenia, complete response <1 year duration, and primary refractory disease. Adults who have disease refractory 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 (National Cancer Institute [NCI], 2017a, NCI, 2017b; National Comprehensive Cancer Network Guidelines™ [NCCN Guidelines™], 2017; Horning, 2008).

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).

A boost of hematopoietic progenitor or stem cells, also referred to as a hematopoietic stem-cell infusion (HSCI) may be used for the following indications: facilitate more rapid hematopoietic recovery or prevent graft loss or loss of chimerism following HSCT. The cell product used for a boost may be a previously cryopreserved cell product that contains stem cells or may alternatively require the donor to undergo additional evaluation, mobilization, and harvest. A boost is not preceded by a preparative regimen, and may be required when additional conventional chemotherapy is given to treat relapse and reestablish remission after transplantation. Prolonged cytopenias and immunosuppression may result, requiring additional HSCI which is typically given days to weeks after reinduction chemotherapy (LeMaistre, 2013).

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

Autologous HSCT

Adult Hodgkin Disease: High-dose chemotherapy and autologous HSCT have 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 relapsed 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, 2017a).

Rancea et al. (2013) published a Cochrane review regarding the effectiveness of high-dose chemotherapy followed by autologous stem cell transplantation for patients with relapsed/refractory Hodgkin lymphoma. The authors included three randomized controlled open-label trials with 14 publications, assessing 398 patients. The number of studies was very low and overall the quality of the trials was rated as moderate. Two trials showed a non-statistically significant trend that high-dose chemotherapy followed by autologous HSCT compared to conventional chemotherapy increases overall survival (OS) (p=0.10); however, the increase in progression-free survival (PFS) was significant for individuals treated with autologous HSCT (p=0.0009). Adverse events were reported in one trial only and did not differ statistically significant between the treatment arms. Conclusions regarding treatment-related mortality (TRM) could not be made because of insufficient evidence (p=0.45). There was no difference in OS between use of sequential high-dose chemotherapy plus autologous HSCT and single high-dose chemotherapy following by autologous HSCT (p=0.816), with three-year OS of 80% and 87%, respectively. A greater number of adverse events and infections were noted in those who underwent sequential high-dose chemotherapy. Data from this systematic review suggest a PFS benefit for patients with relapsed or refractory HL after first-line therapy in those treated with HDCT followed by ASCT compared to patients treated with conventional chemotherapy. A positive but non-significant trend regarding OS was also seen.

A case series 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 Hodgkin Disease:** Therapy for children with low-stage disease that are initially treated with dose-intensive treatment usually includes induction chemotherapy, and high-dose chemotherapy with HSCT therapy for relapse or progression (HSCT) Following autologous HSCT, the projected survival rate is 45% to 70% and progression-free survival is 30% to 89% in selected individuals with primary progressive or relapsed disease (NCI, 2017b; Diehl, 2008).

Outcomes for children with primary refractory HD are poor even with HSCT (NCI, 2017b). 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 hematopoietic stem-cell transplantation (HSCT). Median event-free-survival (EFS) at 22.8 months was 36% and median overall survival (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:** Myeloablative conditioning typically precedes a hematopoietic stem cell transplant. It consists of either chemotherapy or radiation sufficient to destroy the myeloid cells other than red blood cells.
and platelets. Although autologous 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, 2017a; Akpek, 2001; Nachbaur, 2001). The probability of relapse with allogeneic HSCT was 30%–34%, compared with 38%–51% with autologous HSCT in two retrospective studies, suggesting the existence of a graft-versus-lymphoma effect (Akpek, 2001; Nachbaur, 2001). A limitation of allogeneic HSCT is the relatively high rate of transplantation-related mortality (TRM), usually associated with graft-versus-host-disease (GVHD) and infection. Nonetheless, myeloablative allogeneic HSCT is an accepted treatment option for an individual who is not a candidate for autologous HSCT.

A systematic review and meta-analysis published by Rashidi et al. (2016) reported outcomes of 38 studies (42 reports) involving 1850 patients. The primary endpoints were six-month, one-year, two-year and three-year relapse-free survival (RFS) and overall survival (OS). The pooled estimates for RFS were 77%, 50%, 37% and 31% at six months and one, two and three years, respectively. The corresponding outcomes for OS were 83%, 68%, 58% and 50%, respectively. Pooled estimates for cumulative incidence of relapse was 15%, 34%, 42% and 46%, respectively. The corresponding numbers for non-relapse mortality were 13%, 19%, 19% and 19%, respectively. Conditioning was myeloablative in seven studies, reduced intensity in 30 and mixed or unknown in the remaining studies. The median follow-up of patients ranged between 11 and 104 months. On multivariate analysis previous autologous HSCT was independently associated with higher one-year (p = 0.012) and two-year (p = 0.040) OS, higher one-year RFS (p = 0.005), and lower one-year (p < 0.001) and two-year (p = 0.037) NRM. Chemosensitive relapse was independently associated with higher two-year OS (p = 0.047) and one-year RFS (p = 0.016). Data suggests that non-durable remissions are a major shortcoming of allogeneic HSCT in Hodgkin lymphoma. The authors noted that the role of allogeneic HSCT may change as drugs with novel mechanisms of action continue to be developed.

**Nonmyeloablative conditioning:** 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. The use of nonmyeloablative conditioning and allogeneic HSCT has been proposed for the treatment of selected individuals with HD.

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 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 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.
Hayes, Inc. published a Technology Brief regarding tandem autologous stem-cell transplantation for Hodgkin disease and noted that limited prospective uncontrolled trial data suggest that there are some positive clinical and survival benefits for these patients who have limited options. Although there is the possibility of some beneficial effects of tandem ASCT in patients with refractory or relapsed HL, the overall quality of the body of evidence is low. Interpretation of the data is complicated by differences between the studies in patient inclusion criteria, length and extent of follow-up, induction, and HDC regimens, methods for stem cell collection and the quantity infused, use of irradiation, timing of ASCT, and interval between the first and second ASCT (2015; reviewed 2017).

Although there are several published peer-reviewed cohort studies, limitations include 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.

**Professional Societies/Organizations**

**American Society for Blood and Marrow Transplantation (ASBMT):** The ASBMT guidelines regarding the role of cytotoxic therapy with hematopoietic cell transplantation in the treatment of Hodgkin lymphoma noted that autologous HSCT should not be performed as up-front consolidation even inpatients with high-risk or advanced disease (Perales, et al., 2015).

**National Marrow Donor Program (NMDP)/American Society for Blood and Marrow Transplantation (ASBMT):** For Hodgkin lymphoma, hematopoietic stem-cell transplantation (HSCT) referral guidelines recommend referral for individuals in primary induction failure or relapse and for those in second or subsequent remission (1996-2016).

**National Cancer Institute (NCI) (2017a; 2017b):** In their discussion of recurrent adult HL, NIC noted that adult patients who relapse after initial combination chemotherapy can 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. 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. Reduced-intensity conditioning for allogeneic stem cell transplantation is under clinical evaluation.

- Childhood or adolescent primary refractory or recurrent HD
  - Myeloablative chemotherapy with autologous HCT is the recommended approach for patients who develop refractory disease during therapy or relapsed disease within 1 year after completing therapy
  - Autologous HCT has been preferred for patients with relapsed Hodgkin lymphoma because of the historically high transplant-related mortality (TRM) associated with allogeneic transplantation
  - Allogeneic HCT has been used with encouraging results for patients who fail after autologous HCT or for patients with chemoresistant disease
  - Reduced-intensity allogeneic transplantation that typically uses fludarabine or low-dose total body irradiation to provide a nontoxic immunosuppression has demonstrated acceptable rates of TRM.

**National Comprehensive Cancer Network Guidelines™ (NCCN):** The NCCN guideline for Hodgkin Lymphoma (2017) included high-dose therapy and autologous stem cell rescue as a recommended second-line treatment option for refractory disease. NCCN stated that there is major disagreement re the use of allogeneic HSCT for select patients with refractory or relapsed disease. Autologous HSCT is the best option for patients that are not cured by primary treatment even though it doesn’t improve overall survival.

**Use Outside of the US**

**British Committee Standards in Haematology/British Society of Blood and Marrow Transplantation:** Collins et al. (2014) published guidelines for the management of primary resistant and relapsed classical Hodgkin lymphoma. The Guidelines included the following:
• Autologous stem-cell transplant (ASCT) is the standard treatment for patients with primary resistant disease and relapsed disease who achieve an adequate response to salvage therapy.
• ASCT is not recommended in those failing to achieve an adequate response.
• Tandem ASCT cannot currently be recommended outside of clinical trials.
• Allogeneic transplantation using a reduced intensity conditioning regimen is the treatment of choice for younger patients with a suitable donor and chemo-sensitive disease following failure of ASCT.
• An appropriately human leucocyte antigen (HLA)-matched unrelated donor should be considered when there is no HLA-matched sibling.
• A second autologous transplant is a reasonable clinical option in selected patients with late relapse following ASCT.

Italian Society of Hematology, Italian of Experimental Hematology, and Italian Group for Bone Marrow Transplantation: The 2009 Guideline on the initial work-up, management and follow-up of classical Hodgkin lymphoma noted that individuals younger than age 60–65 with relapsed disease or refractory to first-line therapy should receive second-line therapy for debulking, followed by autologous transplantation in chemo-sensitive patients. An allogeneic HSCT is recommended in patients relapsing after autologous transplantation and in those refractory to one–two lines of chemotherapy or with early relapses, who fail to collect a suitable number of autologous stem-cells. A reduced-intensity conditioning is recommended (Brusomolino et al., 2009).

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

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<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic</td>
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<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous</td>
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<td>Transplant preparation of hematopoietic progenitor cells; tumor cell depletion</td>
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<td>38214</td>
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<td>Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer</td>
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<td>S2150</td>
<td>Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre and post transplant care in the global definition</td>
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References


