Cigna Medical Coverage Policy

Subject **Stem-Cell Transplantation for Hodgkin Disease**

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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 an appropriately-matched human leukocyte antigen (HLA) donor 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 an appropriately -matched HLA donor 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 HSCT

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 (National Cancer Institute [NCI], 2013a, NCI, 2013b; National Comprehensive Cancer Network Guidelines™ [NCCN Guidelines™], 2013; Horning, 2008). 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, leukocytosis, lymphocytopenia, complete response <1 year duration, and primary refractory disease (NCI, 2013a; NCI, 2013b; NCCN, 2013). 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.

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 to facilitate more rapid hematopoietic recovery, 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 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 (Engert, 2011). 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, 2012a).

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 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 HSCT therapy for relapse or progression (HSCT) (NCI, 2012b). 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, 2012b). 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: 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, 2012a; Akpek, 2001; Nachbaur, 2001), with 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). However, 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.

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. 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.

Professional Societies/Organizations
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 (2014).

National Cancer Institute (NCI) (2014a; 2014b): Regarding advanced, unfavorable Hodgkin disease (HD) in adults the NCI (2014a) 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.” For recurrent HD in adults the NCI notes “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 disease-free survival (DFS) rate of 27% to 48%.” The use of human leukocyte antigen-matched sibling marrow (allogeneic transplantation) results in a lower relapse rate, but the benefit may be offset by increased toxic effects. Reduced-intensity conditioning for allogeneic stem cell transplantation is also under clinical evaluation. 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 hematopoietic stem-cell transplantation (HSCT) for children and adolescents with primary progressive/recurrent HD, the NCI (2014b) notes “Myeloablative chemotherapy with autologous hematopoietic cell transplantation (HCT) is the recommended approach for patients who develop refractory disease during therapy or relapsed disease within one year after completing therapy. In addition, this approach is also recommended for those who recur with extensive disease after the first year of completing therapy or for

those who recur after initial therapy that included intensive (alkylating agents and anthracyclines) multiagent chemotherapy and radiation 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." The projected survival rate is 45% to 70% and progression-free survival is 30% to 89% following autologous HCT. Regarding the use of allogeneic HSCT for children with primary refractory/recurrent HD, the NCI notes that allogeneic HSCT has been used with encouraging results for patients who fail following autologous HCT or for patients with chemoresistant disease. Investigations of reduced-intensity allogeneic transplantation have demonstrated acceptable rates of TRM.

National Comprehensive Cancer Network Guidelines™ ([NCCN Guidelines™], 2013): Regarding treatment of refractory disease or relapse the NCCN Practice Guidelines in Oncology for Hodgkin Disease algorithm notes that high dose therapy is indicated for refractory disease as second line therapy. The Guidelines also note that allogeneic stem cell transplant (SCT) with myeloablative conditioning has been associated with lower relapse rates in patients with relapsed or refractory disease; however, treatment-related mortality is more than 50%. Allogeneic SCT with reduced intensity conditioning has been reported to have decreased rates of TRM; however the NCCN notes that this approach remains investigational. Autologous stem-cell rescue and high-dose chemotherapy is the best treatment option for progressive or relapsed disease, although overall survival is not improved.

Use Outside of the US: Italian Society of Hematology, Italian of Experimental Hematology, and Italian Group for Bone Marrow Transplantation (2009): Guidelines published by Brusomolino et al. (2009) on behalf of these three groups note 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 chemosensitive 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.

Summary
Although data are not robust regarding improved overall survival autologous hematopoietic stem-cell transplantation (HSCT) is considered a component of the standard of care for selected individuals with refractory, primary progressive or recurrent Hodgkin disease (HD). Myeloablative allogeneic HSCT is also considered an acceptable treatment option for selected individuals who are not eligible for autologous HSCT. For selected individuals with relapsed or refractory Hodgkin disease after prior HSCT, nonmyeloablative conditioning and allogeneic HSCT is also a reasonable treatment option. The role of tandem HSCT for the treatment of HD has not yet been established.

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

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, per donor
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor

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, allogeneic
38232	Bone marrow harvesting for transplantation, autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation, per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
38242	Allogeneic 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 of pre-and post-transplant care in the global definition

References

1. Ahmed T, Rashid K, Waheed F, Kancherla R, Qureshi Z, Hoang A, et al. Long-term survival of patients with resistant lymphoma treated with tandem stem cell transplant. Leuk Lymphoma. 2005 Mar;46(3):405-14.

2. Akhtar S, Abdelsalam M, El Weshi A, Al Husseini H, Janabi I, Rahal M, et al. High-dose chemotherapy and autologous stem cell transplantation for Hodgkin's lymphoma in the kingdom of Saudi Arabia: King Faisal specialist hospital and research center experience. Bone Marrow Transplant. 2008 Aug;42 Suppl 1: S37-S40.

3. Akpek G, Ambinder RF, Piantodosi S, Abrams RA, Brodsky RA, Vogelsang GB, et al. Long-term results of blood and marrow transplantation for Hodgkin's lymphoma. J Clin Oncol. 2001 Dec 1;19(23):4314-21.

4. Alvarez I, Sureda A, Cabellero MD, Urbano-Ispizua A, Ribera JM, Canales M, et al. Nonmyeloablative stem cell transplantation is an effective therapy for refractory or relapsed Hodgkin lymphoma: results of a Spanish Prospective Cooperative Protocol. Biol Blood Marrow Transplant. 2006 Feb;12(2):172-83.

5. Anderlini P, Saliba R, Acholonu S, Giralt SA, Andersson B, Ueno NT, et al. Fludarabine-melphalan as a preparative regimen for reduced-intensity conditioning allogeneic stem cell transplantation in relapsed and refractory Hodgkin's lymphoma: the updated M.D. Anderson Cancer Center experience. Haematologica. 2008 Feb;93(2):257-64. Epub 2008 Jan 26.

6. Anderlini P, Saliba R, Acholonu S, Okoroji GJ, Donato M, Giralt S, et al. Reduced-intensity allogeneic stem cell transplantation in relapsed and refractory Hodgkin's disease: low transplant-related mortality and impact of intensity of conditioning regimen. Bone Marrow Transplant. 2005;35:943-51.

7. Andre M, Henry-Amar M, Pico JL, Brice P, Blaise D, Kuentz M, et al. Comparison of high-dose therapy and autologous stem-cell transplantation with conventional therapy for Hodgkin's disease induction failure: a case-control study. J Clin Oncol. 1999 Jan;17(1):222-9.

8. Arranz SR, Iriondo A, Carreras E, Lahuerta JJ, Garcia-Conde J, Jarque I, et al. Autologous stem-cell transplantation for Hodgkin's disease: results and prognostic factors in 494 patients from the Grupo Espanol de Linfomas/Transplante Autologo de Medula Osea Spanish Cooperative Group. J Clin Oncol. 2001 Mar 1;19(5):1395-404.

9. Baron F, Storb R, Storer BE, Maris MB, Niederweiser D, Shizuri JA, et al. Factors associated with outcomes in allogeneic hematopoietic cell transplantation with nonmyeloablative conditioning after failed myeloablative hematopoietic cell transplantation. J Clin Oncol. 2006 Sep 1;24(25):4150-7. Epub 2006 Aug 8.

10. Benekli M, Smiley SL, Younis T, Czuczman MS, Hernandez-Ilizaliturri F, Bambach B, et al. Intensive conditioning regimen of etoposide (VP-16), cyclophosphamide and carmustine (VCB) followed by autologous hematopoietic stem cell transplantation for relapsed and refractory Hodgkin's lymphoma. Bone Marrow Transplant. 2008 Apr;41(7):613-9. Epub 2007 Dec 10.

11. Brusamolino E, Bacigalupo A, Barosi G, Biti G, Gobbi PG, Levis A, et al. Classical Hodgkin's lymphoma in adults: guidelines of the Italian Society of Hematology, the Italian Society of Experimental Hematology, and the Italian Group for Bone Marrow Transplantation on initial work-up, management, and follow-up. Haematologica. 2009 Apr;94(4):550-65.

12. Brusamolina E, Carella AM. Treatment of refractory and relapsed Hodgkin's lymphoma: facts and perspectives. Haematologica. 2007 Jan;92(1):6-10.

13. Burroughs LM, Maris MB, Sandmaier BM, Leisenring M, Stuart MJ, Niederweiser D, et al. HLA-matched related or unrelated donor non-myeloablative conditioning and hematopoietic cell transplant for patients with advanced Hodgkin's disease. Biol Blood Marrow Transplant. 2004;10(suppl 1):73.

14. Byrne BJ, Gockerman JP. Salvage therapy in Hodgkin's lymphoma. Oncologist. 2007 Feb;12(2):156-67.

15. Castagna L, Magagnoli M, Balzarotti M, Sarina B, Siracusano L, Nozza A, et al. Tandem high-dose chemotherapy and autologous stem cell transplantation in refractory/relapsed Hodgkin's lymphoma: a monocenter prospective study. Am J Hematol. 2007 Feb;82(2):122-7.

16. Claviez A, Klingbiel T, Beyer J, Nurnberger W, Ehninger G, Suttorp M, et al. Allogeneic peripheral blood stem cell transplantation following fludarabine-based conditioning in six children with advanced Hodgkin's disease. Ann Hematol. 2004 Apr;83(4):237-41.

17. Constans M, Sureda A, Terol MJ, Arranz R, Caballero MD, Irionda A, et al. Autologous stem cell transplantation for primary refractory Hodgkin's disease: results and clinical variables affecting outcome. Ann Oncol. 2003;14(5):745-51.

18. Cooney JP, Stiff PJ, Toor AA, Parthasarathy M. BEAM allogeneic transplantation for patients with Hodgkin's disease who relapse after autologous transplantation is safe and effective. Biol Blood Marrow Transplant. 2003 Mar;9(3):177-82.

19. Czyz J, Dziadziuszko R, Knopinska-Postuszuy W, Hellmann A, Kachel L, Holowiecki J, et al. Outcome and prognostic factors in advanced Hodgkin's disease treated with high-dose chemotherapy and autologous stem cell transplantation: a study of 341 patients. Ann Oncol. 2004;15:1222-30.

20. Devetten MP, Hari PN, Carreras J, Logan BR, van Biesen K, Bredeson CN, et al. Unrelated donor reduced-intensity allogeneic hematopoietic stem cell transplantation for relapsed and refractory Hodgkin lymphoma. Biol Blood Marrow Transplant. 2009 Jan;15(1):109-17.

21. ECRI Institute. High Dose Chemotherapy with Allogeneic Stem Cell Transplantation for Hodgkin's Disease. Plymouth Meeting (PA): ECRI Institute Health Technology Assessment Information Service; 2002 Mar. 29 (Evidence Report: no. 68). Available at URL address: http://www.ecri.org

22. Engert A, Eichenauer DA, Harris NL, Mauch PM, Diehl V. Hodgkin lymphoma. In: DeVita, Jr. VT, Lawrence TS, Rosenberg SA, editors. DeVita, Hellman and Rosenberg's Cancer: Principles & Practice of Oncology. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2011.

23. Ferme C, Mounier N, Divine M, Brice P, Stamatoullas A, Reman O, et al. Intensive salvage therapy with high-dose chemotherapy for patients with advanced Hodgkin's disease in relapse or failure after initial chemotherapy: results of the Group d'Etudes des Lymphomes de l'Adulte H89 Trial. J Clin Oncol. 2002 Jan 15;20(2):467-75.

24. Forrest DL, Hogge DE, Nevill TJ, Nantel SH, Barnett MJ, Sheperd JD, et al. High-dose therapy and autologous hematopoietic stem-cell transplantation does not increase the risk of second neoplasms for patients with Hodgkin's lymphoma: a comparison of conventional therapy alone versus conventional therapy followed by autologous hematopoietic stem-cell transplantation. J Clin Oncol. 2005 Nov 1;23(31):7994-8002. Epub 2005 Oct 3.

25. Fung HC, Stiff P, Schriber J, Toor A, Smith E, Rodriguez T, et al. Tandem autologous stem cell transplantation for patients with primary refractory or poor risk recurrent Hodgkin lymphoma. Biol Blood Marrow Transplant. 2007 May;13(5):594-600. Epub 2007 Mar 23.

26. Horning SJ. Hodgkin's lymphoma. In: Abeloff MD, Armitage JO, Niederhuber JE, Kastan MB, McKenna WG, editors. Clinical Oncology. 4th ed. New York: Churchill Livingstone;2008.

27. Josting A, Nogova L, Franklin J, Glossmann JP, Eich HT, Sieber M, et al. Salvage radiotherapy in patients with relapsed and refractory Hodgkin's lymphoma: a retrospective analysis from the German Hodgkin Lymphoma Study Group. J Clin Oncol. 2005;23:1522-9.

28. LeMaistre CF, Farnia S, Crawford S, McGuirk J, Maziarz RT, Coates J, et al. Standardization of terminology for episodes of hematopoietic stem cell patient transplant care. Biol Blood Marrow Transplant. 2013 Jun;19(6):851-7. Epub 2013 Mar 21

29. Leukemia & Lymphoma Society, The. Hodgkin lymphoma. Updated 2012 March 15. Accessed Sep 13, 2013. Available at URL address: http://www.leukemia-lymphoma.org/all_page?item_id=7085

30. Lieskovsky YE, Donaldson SS, Torres MA, Wong RM, Amylon MD, Link MP, Agarwal R. High-dose therapy and autologous hematopoietic stem-cell transplantation for recurrent or refractory pediatric Hodgkin's disease: results and prognostic indices. J Clin Oncol. 2004 Nov 15;22(22):4532-40.

31. National Cancer Institute. Adult Hodgkin's Lymphoma Treatment (PDQ®). [a]. Updated 2014 February 28. Accessed Sep 3, 2014. Available at URL address: http://www.cancer.gov/cancertopics/pdq/treatment/adulthodgkins/HealthProfessional

32. National Cancer Institute. Childhood Hodgkin Lymphoma Treatment (PDQ®). [b] Updated 2014 August 22. Accessed Sep 3, 2014. Available at URL address: http://www.cancer.gov/cancertopics/pdq/treatment/childhodgkins/HealthProfessional

33. National Comprehensive Cancer Network® (NCCN). NCCN GUIDELINES™ Clinical Guidelines in Oncology™. © v.2. 2014 Hodgkin lymphoma. National Comprehensive Cancer Network, Inc 2013, All Rights Reserved. Accessed Sep 3, 2014. Available at URL address: http://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf

34. National Marrow Donor Program. Transplant referral timing guidelines: Hodgkin's lymphoma. © 1996-2013. Accessed Sep 3, 2014. Available at URL address: https://bethematchclinical.org/Transplant-Indications-and-Outcomes/Referral-Timing-Guidelines/

35. Peggs KS, Hunter A, Chopra R, Parker A, Mahendra P, Milligan D, et al. Clinical evidence of a graft-versus-Hodgkin's-lymphoma effect after reduced-intensity allogeneic transplantation. Lancet. 2005 Jun 4-10;365(9475):1934-41.

36. Rancea M, Monsef I, von Tresckow B, Engert A, Skoetz N. High-dose chemotherapy followed by autologous stem cell transplantation for patients with relapsed/refractory Hodgkin lymphoma. Cochrane Database Syst Rev. 2013 Jun 20;6:CD009411.

37. Schellong G, Dorffel W, Claviez A, Korholz D, Mann G, Scheel-Walter HG, et al. Salvage therapy of progressive and recurrent Hodgkin's disease: results from a multicenter study of the Pediatric DAL/GPOH-HD Study Group. J Clin Oncol. 2005 1 Sep;23(25):6181-9.

38. Sirohi B, Cunningham D, Powles R, Murphy F, Arkenau T, Norman A, et al. Long-term outcome of autologous stem-cell transplantation in relapsed or refractory Hodgkin's lymphoma. Ann Oncol. 2008 Jul;19(7):1312-9.

39. Stoneham S, Ashley S, Pinkerton CR, Wallace WH, Shankar AG; United Kingdom Children's Cancer Study Group. Outcome after autologous hematopoietic stem cell transplantation in relapsed or refractory childhood Hodgkin disease. J Pediatr Hematol Oncol. 2004 Nov;26(11):740-5.

40. Sureda A, Robinson S, Canals C, Carella AM, Boogaerts MA, Cabarello D. Reduced-intensity conditioning compared with conventional allogeneic stem-cell transplantation in relapsed or refractory Hodgkin's lymphoma: an analysis from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol. 2008 Jan 20;26(3):455-62. Epub 2007 Dec 17.

41. Todisco E, Castagna L, Sanna B, Mazza R, Anastasia A, Balzorotti M, et al. Reduced-intensity allogeneic transplantation in patients with refractory or progressive Hodgkin's disease after high-dose chemotherapy and autologous stem-cell infusion. Eur J Haematol. 2007 Jan 23;[Epub ahead of print]

42. Wadehra N, Farag S, Bolwell B, Elder P, Penza S, Kalaycio M, et al. Long-term outcome of Hodgkin disease patients following high-dose busulfan, etoposide, cyclophosphamide, and autologous stem cell transplantation. Biol Blood Marrow Transplant. 2006 Dec;12(12):1343-9.

43. Zinzani PL, Tani M, Gabriele A, Gherlinzoni F, de Vivo A, Ricci P, et al. High-dose therapy with autologous transplantation for Hodgkin's disease: the Bologna experience. Haematologica. 2003 May;88(5):522-8.