Subject: Hematopoietic Stem Cell Transplantation for Hodgkin's and Non-Hodgkin's Lymphoma	**Original Effective Date:** 4/24/13
Policy Number: MCP-125	**Revision Date(s):** 6/2/15, 9/21/16, 12/10/19
Review Date: 12/16/15, 9/21/16, 9/19/17, 3/8/18, 12/10/19	
MCPC Approval Date: 3/8/18, 12/10/19	

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina Clinical Policy (MCP) document and provide the directive for all Medicare members.[1]

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

Lymphoma:

Lymphomas are neoplasms of the lymphatic system, which is a network of blood-filtering tissues that help fight infection and disease and are found in the lymph nodes, spleen, thymus gland, adenoids, tonsils, and bone marrow. In particular, lymphoma affects lymphocytes, specialized white blood cells that are responsible for immunity. The two major types of lymphoma are Hodgkin's disease, which is distinguished by the presence of so-called Reed-Sternberg cells, and non-Hodgkin's lymphoma (NHL).

Non-Hodgkin lymphoma or NHL is defined as any of a large group of cancers of lymphocytes (white blood cells). Non-Hodgkin lymphomas can occur at any age and are often marked by lymph nodes that are larger than normal, fever, and weight loss. There are many different types of non-Hodgkin lymphoma. These types can be divided into aggressive (fast-growing) and indolent (slow-growing) types, and they can be formed from either B-cells or T-cells. B-cell non-Hodgkin lymphomas include Burkitt lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), diffuse large B-cell lymphoma, follicular lymphoma, immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, and mantle cell lymphoma. T-cell non-Hodgkin lymphomas include mycosis fungoides, anaplastic large cell lymphoma, and precursor T-lymphoblastic lymphoma. Lymphomas that occur after bone marrow or stem cell transplantation are usually B-cell non-Hodgkin lymphomas. Prognosis and treatment depend on the stage and type of disease. NHL can be further divided into two prognostic groups: the indolent lymphomas and the aggressive lymphomas. Indolent NHL types have a relatively good prognosis with a median survival as long as 10 years, but they usually are not

curable in advanced clinical stages. Early-stage (stage I and stage II) indolent NHL can be effectively treated with radiation therapy alone. Most of the indolent types are nodular (or follicular) in morphology. The aggressive type of NHL has a shorter natural history, but a significant number of these patients can be cured with intensive combination chemotherapy regimens. In general, with modern treatment of patients with NHL, overall survival at 5 years is approximately 50% to 60%. Of patients with aggressive NHL, 30% to 60% can be cured. The vast majority of relapses occur in the first 2 years after therapy. The risk of late relapse is higher in patients with a divergent histology of both indolent and aggressive disease.

Hodgkin lymphoma or Hodgkin disease is a cancer of the immune system that is marked by the presence of a type of cell called the Reed-Sternberg cell. The two major types of Hodgkin lymphoma are classical Hodgkin lymphoma and nodular lymphocyte-predominant Hodgkin lymphoma. Symptoms include the painless enlargement of lymph nodes, spleen, or other immune tissue. Other symptoms include fever, weight loss, fatigue, or night sweats. There are three distinct forms of Hodgkin lymphoma: The childhood form occurs in individuals aged 14 years and younger. The childhood form of Hodgkin lymphoma increases in prevalence in association with larger family size and lower socioeconomic status. Early exposure to common infections in preschool appears to decrease the risk of Hodgkin lymphoma, most likely by maturation of cellular immunity. The young adult for effects individuals aged 15 to 34 years. The young adult form is associated with a higher socioeconomic status in industrialized countries, increased sibship size, and earlier birth order. The lower risk of Hodgkin lymphoma observed in young adults with multiple older, but not younger, siblings is consistent with the hypothesis that early exposure to viral infection (which the siblings bring home from school, for example) may play a role in the pathogenesis of the disease. The older adult form most commonly presents in individuals aged 55 to 74 years.

Stem Cell Transplantation

Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSCs) from a donor into a patient. HSCs are immature cells that can develop into any of the three types of blood cells (red cells, white cells or platelets). HSCs are created in the bone marrow and are found in the bone marrow and peripheral blood. There is also a high concentration of HSCs in umbilical-cord blood. Hematopoietic stem-cell transplantation (HSCT) can be either autologous (using the person's own stem cells) or allogeneic (using stem cells from a donor). In allogeneic HSCT, it is preferable for donors to have a human leukocyte antigen (HLA) type that is identical to the recipient. Matching is performed on the basis of variability at three of more loci of the HLA gene (e.g., HLA-A, HLA-B, HLA-DRB1). As HLA variability increases, transplant-related morbidity and mortality, including graft rejection and graft-versus-host disease, also increase. For patients who lack an HLA-matched sibling, alternative sources of donor grafts include suitably HLA-matched adult unrelated donors, umbilical cord blood stem cells, and partially HLA-mismatched, or HLA-haploidentical, related donors.

RECOMMENDATION

All transplants require prior authorization from the Corporate Transplant Department. Solid organ transplant requests will be reviewed by the Corporate Senior Medical Director or qualified clinical designee. All other transplants will be by the Corporate Senior Medical Director or covering Medical Director. If the criteria are met using appropriate NCD and/or LCD guidelines, state regulations and/or MCP policies the Corporate Senior Medical Director's designee can approve the requested transplant.

Members must meet UNOS guidelines for transplantation and the diagnosis must be made by a *Specialist in the Disease* and or Transplant Surgeon.

Pre-Transplant Evaluation:

Criteria for transplant evaluation include all of the following: [5 31 32 37 40]

- ❑ History and physical examination
- ❑ Psychosocial evaluation and clearance:
  - No behavioral health disorder by history or psychosocial issues:
    - ➢ if history of behavioral health disorder, no severe psychosis or personality disorder
    - ➢ mood/anxiety disorder must be excluded or treated
    - ➢ member has understanding of surgical risk and post procedure compliance and follow-up required
  - Adequate family and social support
- ❑ EKG
- ❑ Chest x-ray
- ❑ Cardiac clearance in the presence of any of the following:
  - o chronic smokers
  - o > 50 years age
  - o those with a clinical or family history of heart disease or diabetes
- ❑ Pulmonary clearance if evidence of pulmonary artery hypertension (PAH) or chronic pulmonary disease
- ❑ Performance Status [5]: [ONE]
  - o Karnofsky score 70-100%
  - o Eastern Cooperative Oncology Group (ECOG) grade 0-2
- ❑ Neurological exam and clearance for transplant: [ONE]
  - o Normal exam by H&P
  - o Abnormal neurological exam with positive findings: [ONE]
    - ➢ Lumbar puncture normal cytology
    - ➢ Lumbar puncture with cytological exam abnormal: CNS disease treated prior to clearance
- ❑ Lab studies:
  - o *Complete blood count, Kidney profile (blood urea nitrogen, creatinine), electrolytes, calcium, phosphorous, albumin, liver function tests, Coagulation profile (prothrombin time, and partial thromboplastin time)
  - o *Serologic screening for HIV, Epstein Barr virus (EBV), Hepatitis virus B (HBV), and Hepatitis C(HCV), cytomegalovirus (CMV), RPR and/or FTA:
    - If HIV positive all of the following are met:
      - ➢ CD4 count >200 cells/mm-3 for >6 months
      - ➢ HIV-1 RNA undetectable
      - ➢ On stable anti-retroviral therapy >3 months

- No other complications from AIDS (e.g., opportunistic infection, including aspergillus, tuberculosis, coccidioides mycosis, resistant fungal infections, Kaposi's sarcoma, or other neoplasm)
  - If abnormal serology need physician plan to address and/or treatment as indicated
- UDS (urine drug screen) if patient is current or gives a history of past drug abuse

❑ *Colonoscopy (if indicated or if patient is 50 ≥ older should have had an initial screening colonoscopy, after initial negative screening requires follow up colonoscopy every ten years) with complete workup and treatment of abnormal results as indicated

❑ *GYN examination with Pap smear for women ≥ 21 to ≤ 65 years of age or indicated (not indicated in women who have had a TAH or TVH) with in the last three year with complete workup and treatment of abnormal results as indicated

Within the last 12 months:

❑ Dental examination or oral exam showing good dentition and oral care or no abnormality on panorex or plan for treatment of problems pre or post-transplant

❑ *Mammogram (if indicated or > age 40) with complete workup and treatment of abnormal results as indicated

❑ *PSA if history of prostate cancer or previously elevated PSA with complete workup and treatment of abnormal results as indicated

Participating Centers of Excellence may waive these criteria

Criteria for Transplantation: [26-42]

Non-Hodgkin's Lymphoma [26-29 31 32 33-37 40]

1. ***Hematopoietic Autologous stem-cell transplantation (AuSCT)*** may be authorized in adults and children for the treatment of acute ***Non-Hodgkin's Lymphoma (NHL)*** when ANY of the following criteria are met:

   ❑ All pre-transplant criteria are met; and
   ❑ Classification of Lymphoma: [ONE]
   - Diffuse large B cell: [ONE] [40]
     - ◊ Relapsed
     - ◊ Treatment refractory or chemosensitive
     - ◊ Double or triple cytogenetic rearrangement (MYC and BCL-2 and/or BCL-6) at diagnosis
   - Mantel cell: [40]
     - ◊ Partial or complete response following induction chemotherapy (ie, consolidation therapy)
   - Burkitt's lymphoma: [ONE] [40]
     - ◊ Relapsed disease
   - Follicular: [ONE] [40]
     - ◊ Histologic transformation to diffuse large B-cell lymphoma with partial or complete response to treatment
     - ◊ Consolidative therapy for patient in second or third remission
     - ◊ Relapsed or refractory disease

- High Grade: [31 32]
  - ◊ C-myc rearrangement at diagnosis
  - ◊ Primary induction failure
  - ◊ First complete remission (CR1)
  - ◊ First relapse
  - ◊ Second complete remission (CR2) or subsequent remission
- Mature T-Cell: [31 32]
  - ◊ First complete remission (CR1)
  - ◊ First relapse
- Other high risk lymphomas: [31 32]
  - ◊ At diagnosis

2. ***Hematopoietic Allogeneic stem-cell transplantation (HSCT)*** from a human leukocyte antigen (HLA)-matched donor [4] (i.e., at least six out of eight match of the HLA-A, HLA-B, HLA-C and HLA-DRB1 markers) or from cord blood when there are no matched siblings or unrelated donors (i.e. at least four out of six match of the HLA-A, HLA-B and HLA-DRB-1 markers) may be authorized in adults and children for the treatment of acute ***Non-Hodgkin's Lymphoma (NHL)*** when ANY of the following criteria are met:

   - ❑ All pre-transplant criteria are met; and
   - ❑ Classification of Lymphoma: [ONE]
     - Diffuse large B cell: [ONE] [37 40]
       - ◊ Chemosensitive relapsed disease
       - ◊ Relapsed disease post Autologous transplant
     - Burkitt's lymphoma: [ONE] [37 40]
       - ◊ Chemosensitive relapsed disease
     - Follicular: [ONE] [37 40]
       - ◊ Histologic transformation to diffuse large B-cell lymphoma; or
       - ◊ Consolidative therapy for patient in second or third remission
     - Cutaneous T-cell Lymphoma (Mycosis Fungoides/Sezary Syndrome: [ONE] [37 40]
       - ◊ Refractory; or
       - ◊ Progressive (eg, stage IIB, III, or IV)
     - Adult T-cell Lymphoma: [40]
       - ◊ With acute or lymphoma subtype responsive to chemotherapy
     - Mantel cell: [40]
       - ◊ In relapse needing second-line therapy (autologous is first-line)

Hodgkin Lymphoma [27-29 31 32 33-37 39 40]

3. ***Hematopoietic Autologous stem-cell transplantation (AuSCT)*** may be authorized in adults and children for the treatment of acute ***Hodgkin's Lymphoma (HL)*** when ANY of the following criteria are met:

   - ❑ All pre-transplant criteria are met; and one or more of the following[ONE]: [40]

- First relapse in chemosensitive disease
- Partial remission after radiotherapy for isolated lesions
- Primary refractory disease

4. ***Hematopoietic Allogeneic stem-cell transplantation (HSCT)*** from a human leukocyte antigen (HLA)-matched donor [4] (i.e., at least six out of eight match of the HLA-A, HLA-B, HLA-C and HLA-DRB1 markers) or haploidentical related donor (sharing a haplotype; having the same alleles at a set of closely linked genes on one chromosome) [39 43 44 45 47 51 52] or from cord blood when there are no matched siblings or unrelated donors (i.e. at least four out of six match of the HLA-A, HLA-B and HLA-DRB-1 markers) may be authorized in adults and children for the treatment of acute ***Hodgkin's Lymphoma (HL)*** when ALL of the following criteria are met: [37 39]

❑ All pre-transplant criteria are met; and one or more [ONE]: [40]
- Biopsy-proven relapse from primary treatment in less than 12 months;
- Refractory to primary treatment;
- Biopsy-proven relapse after autologous transplant;
- Multiple biopsy-proven relapses;

AND

❑ The requesting transplant recipient (NHL/HL Auto/Allo) should not have any of the following **absolute contraindications**:
- Cardiac, pulmonary, and nervous system disease that cannot be corrected and is a prohibitive risk for surgery
- Malignant neoplasm with a high risk for reoccurrence, non-curable malignancy (excluding localized skin cancer)
- Systemic and/or uncontrolled infection
- AIDS (CD4 count < 200cells/mm3)
- Unwilling or unable to follow post-transplant regimen
  - ◊ Documented history of non-compliance
  - ◊ Inability to follow through with medication adherence or office follow-up
- Chronic illness with one year or less life expectancy
- Limited, irreversible rehabilitation potential
- Active untreated substance abuse issues, requires documentation supporting free from addiction for minimally 6 months if previous addiction was present
- No adequate social/family support

❑ The requesting transplant recipient should be evaluated carefully and potentially treated if the following **relative contraindications** are present:
- Irreversible lung disease patients require consultation and clearance by a Pulmonologist prior to consideration of transplantation, this includes the following:
- Smoking, documentation supporting free from smoking for 6 months
- Active peptic ulcer disease
- Active gastroesophageal reflux disease
- CVA with long term impairment that is not amendable to rehabilitation or a patient with CVA/transient ischemic attack within past 6 months
- Obesity with body mass index of >30 kg/m^2 may increase surgical risk

- Chronic liver disease such as Hepatitis B/C/D, or cirrhosis which increases the risk of death from sepsis and hepatic failure requires consultation by a gastroenterologist or hepatologist
- Gall bladder disease requires ultrasound of the gall bladder with treatment prior to transplantation

CONTINUATION OF THERAPY

When extension of a previously approved transplant authorization is requested, review using updated clinical information is appropriate.

- ❑ If Molina Healthcare has authorized prior requests for transplantation, the following information is required for medical review: [ALL]
  - Presence of no absolute contraindication as listed above;
  - History and physical within the last 12 months;
  - Kidney profile within the last 12 months;
  - Cardiac update if history of cardiac disease within two years (≥ 50 years of age);
  - Psychosocial evaluation or update within the last 12 months;
  - Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.

- ❑ If authorized prior requests for transplantation were obtained from another insurer, the following information is required for medical review: [ALL]
  - Authorization letter/documentation from previous insurer;
  - Presence of no absolute contraindication as listed above;
  - History and physical within the last 12 months;
  - Cardiac update if history of cardiac disease within two years (≥ 50 years of age);
  - Psychosocial evaluation or update within the last 12 months;
  - Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.

COVERAGE EXCLUSIONS

- Allogeneic (ablative or non-myeloablative) stem cell transplantation or autologous stem cell transplantation when the above criteria are not met.
- Hematopoietic stem cell collection, storage and freezing for a future unplanned transplant is not covered.
- Tandem autologous hematopoietic autologous (auto-auto) or allogeneic (allo-allo), also known as sequential stem cell transplantation are considered experimental, investigational and unproven due to limited evidence in the peer reviewed medical literature.

SUMMARY OF MEDICAL EVIDENCE [4-29 43-59]

The published medical evidence and outcomes for hematopoietic stem cell transplantation for NHL/HL in children and adults in the United States consists of registry data obtained from transplant centers that perform adult and pediatric transplantation and is available from the United Network for Organ Sharing (UNOS) database. Registry data demonstrates graft survival rates and outcomes for stem cell transplantation based on demographic and clinical information. [3]

Professional Organizations

The National Marrow Donor Program Transplant Referral Guidelines: For Hodgkin lymphoma transplantation (HSCT) referral guidelines recommend referral for individuals who have primary induction failure or relapse and for CR2 or subsequent remission. Non-Hodgkin's lymphoma transplantation (HSCT) referral guidelines recommend referral for individuals based upon the following types: [31-32]

- *Follicular:*
  - Poor response to initial treatment
  - Initial remission duration <24 months
  - First relapse
  - Transformation to diffuse large B-cell lymphoma
- *Diffuse Large B-Cell or High-Grade Lymphoma*
  - Primary induction failure, including residual PET avid disease
  - First relapse
  - CR2 or subsequent remission
  - Double or triple hit (MYC and BCL-2 and/or BCL-6) – at diagnosis
  - Primary CNS lymphoma at diagnosis
- *Mantle Cell*
  - At diagnosis
  - First relapse
  - Bruton's tyrosine kinase (BTK) intolerant or resistant disease
- *Mature T-cell*
  - CR1
  - First relapse
- *Other High-Risk Lymphomas*
  - At diagnosis

American Society for Blood and Marrow Transplantation (2015) Practice Guidelines have indications for Autologous and Allogeneic Hematopoietic Cell Transplantation that may be accessed at: https://www.asbmt.org/practice-resources/practice-guidelines

CODING INFORMATION THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
	Collection Codes
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
	Cell Processing Services
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
	Cell infusion codes
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
38243	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic hematopoietic cellular transplant boost

HCPCS	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 of pre-and post-transplant care in the global definition

ICD-10	Description
C81.70- C81.79	Other classical Hodgkin lymphoma
C82.0-C82.99	Follicular Lymphoma
C83.1-C83.19	Mantle cell lymphoma, unspecified site
C83.30-C83.39	Diffuse large B-cell lymphoma
C83.50-C83.59	Lymphoblastic (diffuse) lymphoma
C83.70-C83.79	Burkitt lymphoma, unspecified site
C85.1-C85.99	Other types on non-Hodgkin lymphoma

RESOURCE REFERENCES

Government Agency

1. Centers for Medicare & Medicaid Services. NCD for Stem Cell Transplantation (Formerly 110.8.1) 110.23. Effective date 1/27/2016. Accessed at: http://www.cms.gov/medicare-coverage-database/
2. National Marrow Donor Program. NHL-HL Transplant Outcomes. Accessed at: https://bethematchclinical.org/Transplant-Indications-and-Outcomes/
3. National Bone Marrow Donor Program HLA Matching Requirements. Accessed at: http://marrow.org/Patient/Transplant_Process/Search_Process/HLA_Matching__Finding_the_Best_Donor_or_Cord_Blood_Unit.aspx

Peer Reviewed Publications

4. C Mackall, T Fry, R Gress, K Peggs, J Storek and A Toubert. Background to hematopoietic cell transplantation, including post-transplant immune recovery. Bone Marrow Transplant 44: 457-462; doi:10.1038/bmt.2009.255 Accessed at:

http://www.nature.com/bmt/journal/v44/n8/full/bmt2009255a.html
5. Eastern Cooperative Oncology Group (ECOG) Performance Status. Accessed at: http://www.ecog.org/general/perf_stat.html
6. Bloor AJ Thomson K et al. High response rate to donor lymphocyte infusion after allogeneic stem cell transplantation for indolent non-Hodgkin lymphoma. Biol Blood Marrow Transplant. 2008. Jan;14(1):50-8.
7. Mackinnon S. American Society of clinical Oncology (ASCO). Donor Lymphocyte Infusion after Allogeneic Stem Cell Transplantation. 2008.
8. Thakar MS, Forman SJ. ASH evidence-based guidelines: is there a role for second allogeneic transplant after relapse? Hematology Am Soc Hematol Educ Program. 2009:414-8.
9. Jaffe E. The 2008 WHO classification of lymphomas: implications for clinical practice and translational research. Hematology Am Soc Hematol Educ Program. 2009 :523-31
10. Ladetto, M, De Marco, F, Benedetti, F, et al. Prospective, multicenter randomized GITMO/IIL trial comparing intensive (R-HDS) versus conventional (CHOP-R) chemoimmunotherapy in high-risk follicular lymphoma at diagnosis: the superior disease control of R-HDS does not translate into an overall survival advantage. Blood. 2008 Apr 15;111(8):4004-13. PMID: 18239086
11. Sebban, C, Mounier, N, Brousse, N, et al. Standard chemotherapy with interferon compared with CHOP followed by high-dose therapy with autologous stem cell transplantation in untreated patients with advanced follicular lymphoma: the GELF-94 randomized study from the Groupe d'Etude des Lymphomes de l'Adulte (GELA). Blood. 2006 Oct 15;108(8):2540-4. PMID: 16835383
12. Deconinck, E, Foussard, C, Milpied, N, et al. High-dose therapy followed by autologous purged stem-cell transplantation and doxorubicin-based chemotherapy in patients with advanced follicular lymphoma: a randomized multicenter study by GOELAMS. Blood. 2005 May 15;105(10):3817-23. PMID: 15687232
13. Lenz, G, Dreyling, M, Schiegnitz, E, et al. Myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission prolongs progression-free survival in follicular lymphoma: results of a prospective, randomized trial of the German Low-Grade Lymphoma Study Group. Blood. 2004 Nov 1;104(9):2667-74. PMID: 15238420
14. Betticher, DC, Martinelli, G, Radford, JA, et al. Sequential high dose chemotherapy as initial treatment for aggressive sub-types of non-Hodgkin lymphoma: results of the international randomized phase III trial (MISTRAL). Ann Oncol. 2006 Oct;17(10):1546-52. PMID: 16888080
15. Ratko, TA, Belinson, SE, Brown, HM, et al. Hematopoietic Stem-Cell Transplantation in the Pediatric Population [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012 Feb. Accessed at: http://www.ncbi.nlm.nih.gov/books/NBK84626/. 2012 Feb. PMID: 22439159
16. Seftel, M, Rubinger, M. The role of hematopoietic stem cell transplantation in advanced Hodgkin Lymphoma. Transfus Apher Sci. 2007 Aug;37(1):49-56. PMID: 17716946
17. Linch, DC, Winfield, D, Goldstone, AH, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. Lancet. 1993 Apr 24;341(8852):1051-4. PMID: 8096958
18. Schmitz, N, Pfistner, B, Sextro, M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. Lancet. 2002 Jun 15;359(9323):2065-71. PMID: 12086759
19. Murphy, F, Sirohi, B, Cunningham, D. Stem cell transplantation in Hodgkin lymphoma. Expert Rev Anticancer Ther. 2007 Mar;7(3):297-306. PMID: 17338650
20. Sureda, A, Robinson, S, Canals, C, et al. 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. PMID: 18086796
21. Sarina, B, Castagna, L, Farina, L, et al. Allogeneic transplantation improves the overall and progression-free survival of Hodgkin lymphoma patients relapsing after autologous transplantation: a retrospective study based on the time of HLA typing and donor availability. Blood. 2010 May 6;115(18):3671-7. PMID: 20220116
22. Morschhauser, F, Brice, P, Ferme, C, et al. Risk-adapted salvage treatment with single or tandem autologous stem-cell transplantation for first relapse/refractory Hodgkin's lymphoma: results of the prospective multicenter H96 trial by the GELA/SFGM study group. J Clin Oncol. 2008 Dec 20;26(36):5980-7. PMID: 19018090

23. Monjanel H, Deconinck E, Perrodeau E et al. Long-term follow-up of tandem high-dose therapy with autologous stem cell support for adults with high-risk age-adjusted international prognostic index aggressive non-Hodgkin Lymphomas: a GOELAMS pilot study. Biol Blood Marrow Transplant. 2011 Jun;17(6):935-40. doi: 10.1016/j.bbmt.2010.11.017. Epub 2010 Nov 23.
24. Fung, HC, Stiff, P, Schriber, J, 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. PMID: 17448919
25. Castagna L, Magagnoli M, Balzarotti M 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.

Cochrane Reviews

26. Greb, A, Bohlius, J, Schiefer, D, Schwarzer, G, Schulz, H, Engert, A. High-dose chemotherapy with autologous stem cell transplantation in the first line treatment of aggressive non-Hodgkin lymphoma (NHL) in adults. Cochrane Database Syst Rev. 2008(1):CD004024. PMID: 18254036
27. Schaaf, M, Reiser, M, Borchmann, P, Engert, A, Skoetz, N. High-dose therapy with autologous stem cell transplantation versus chemotherapy or immuno-chemotherapy for follicular lymphoma in adults. Cochrane Database Syst Rev. 2012;1:CD007678. PMID: 22258971
28. Schlaak M, Pickenhain J, Theurich S et al. Allogeneic stem cell transplantation versus conventional therapy for advanced primary cutaneous T-cell lymphoma. Cochrane Database Syst Rev. 2013. DOI: 10.1002/14651858.CD008908.pub3
29. Rancea M, Monsef I, von Tresckow B et al. High-dose chemotherapy followed by autologous stem cell transplantation for patients with relapsed/refractory Hodgkin lymphoma. Cochrane Database Syst Rev. 2013. DOI: 10.1002/14651858.CD009411.pub2

Professional Society Guidelines

30. Imrie K, Rumble RB, Crump M, Advisory Panel on Bone Marrow and Stem Cell Transplantation, Hematology Disease Site Group. Stem cell transplantation in adults: recommendations. Toronto (ON): Cancer Care Ontario Program in Evidence-based Care; 2009 Jan 30. 78p.
31. National Marrow Donor Program® (NMDP) and the American Society for Blood and Marrow Transplantation (ASBMT) referral guidelines: Recommended Timing for Transplant Consultation. Accessed at: https://bethematchclinical.org/Transplant-Indications-and-Outcomes/Referral-Timing-Guidelines/
32. National Marrow Donor Program® (NMDP). Patient Eligibility for HCT. Accessed at: https://bethematchclinical.org/Transplant-Indications-and-Outcomes/Eligibility/
33. National Bone Marrow Donor Program. Measuring Engraftment. Accessed at: http://marrow.org/Patient/Transplant_Process/Days_0-30/Measuring_Engraftment.aspx
34. The American Society for Blood and Marrow Transplantation (ASBMT): Guidelines and statements: Accessed at: https://www.asbmt.org/practice-resources/practice-guidelines
    - Majhail NS, Farnia SH, Carpenter PA, Champlin RE, Crawford S, Marks DI, et al. Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2015 Nov;21(11):1863-1869.
    - Role of Cytoxic Therapy with Hematopoietic Stem Cell Transplantation in the treatment of Diffuse Large B Cell Lymphoma: Update of the 2001 Evidence Based Review. Biol Blood Marrow Transplant 17:18-19, 2011.
    - The Role of Cytoxic Therapy with Hematopoietic Stem Cell Transplantation in the treatment of Follicular Lymphoma. Biol Blood Marrow Transplant 17:190-191, 2011.
35. National Cancer Institute. [Website]: Updated 2019.
    - Adult Hodgkin's Lymphoma Treatment. Accessed at: http://www.cancer.gov/types/lymphoma/hp/adult-hodgkin-treatment-pdq
    - Adult non-Hodgkin lymphoma treatment. Accessed at: http://www.cancer.gov/types/lymphoma/hp/adult-nhl-treatment-pdq

- Childhood Hodgkin's lymphoma Treatment. Accessed at: http://www.cancer.gov/types/lymphoma/hp/child-hodgkin-treatment-pdq
- Childhood Non-Hodgkin Lymphoma Treatment. Accessed at: http://www.cancer.gov/types/lymphoma/hp/child-nhl-treatment-pdq

36. National Comprehensive Cancer Network (NCCN) [Website]:
    - Clinical Practice Guidelines in Oncology. Hodgkin lymphoma. V2.2019. Accessed at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
    - Clinical Practice Guidelines in Oncology. Non-Hodgkin's Lymphomas. B-Cell Lymphomas. v5.2019. Accessed at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

Other Resources

37. McKesson InterQual Criteria for Procedures: Adult 2018 InterQual Transplantation, Allogeneic Stem Cell, Autologous Stem Cell; 2018.
38. DynaMed LLC [website]. Non-Hodgkin's Lymphoma. Updated 2019.
39. UpToDate. [website]. Waltham, MA: Walters Kluwer Health; 2019.
    - Holmberg L, Deeg H, Sandmaier. Determining eligibility for autologous hematopoietic cell transplantation.
    - Cannellos GP, Mauch PM.
        - Hematopoietic cell transplantation in classical Hodgkin lymphoma.
        - Relapse of classical Hodgkin lymphoma after initial radiotherapy.
    - Freedman AS, Friedberg JW:
        - Hematopoietic cell transplantation in follicular lymphoma.
        - Treatment of relapsed or refractory diffuse large B cell lymphoma.
        - Initial treatment of mantel cell lymphoma.
        - Treatment of Burkitt leukemia/lymphoma in adults.
    - Jacobsen E, Freedman AS. Treatment of relapsed or refractory peripheral T cell lymphoma.
    - Hoppe RT, Kim YH. Treatment of advanced stage (IIB to IV) mycosis fungoides and Szary syndrome.
    - Fuchs E, Luznik L. HLA-haploidentical hematopoietic cell transplantation.
40. MCG Criteria. Medical Oncology GRG. 2019.
41. Advanced Medical Review (AMR):
    - Policy reviewed by MD board certified in Internal Medicine, Oncology and Hematology. March, 2013.
    - Policy reviewed by a practicing MD board certified in Hematology, Oncology. Nov, 2019.
42. Hayes Technology Brief. Tandem Autologous Stem Cell Transplantation for Hodgkin Lymphoma. Winifred Hayes Inc. Lansdale, PA. June, 2016, last update 2017. [Archived 2018].

2019 Literature Review

43. Ahmed S, Kanakry JA et al. Lower Graft-versus-Host Disease and Relapse Risk in Post-Transplant Cyclophosphamide-Based Haploidentical versus Matched Sibling Donor Reduced-Intensity Conditioning Transplant for Hodgkin Lymphoma. Biol Blood Marrow Transplant. 2019 Sep;25(9):1859-1868.
44. Bazarbachi A, Boumendil A, et al. Influence of donor type, stem cell source and conditioning on outcomes after haploidentical transplant for lymphoma - a LWP-EBMT study. Br J Haematol. 2019 Sep 9.
45. Gauthier J, Castagna L, Garnier F, et al. Reduced-intensity and non-myeloablative allogeneic stem cell transplantation from alternative HLA-mismatched donors for Hodgkin lymphoma: A study by the French Society of Bone Marrow Transplantation and Cellular Therapy. Bone Marrow Transplant. 2017;52(5):689-696.
46. Gauthier J, Poiré X, Gac AC, et al. Better outcome with haploidentical over HLA-matched related donors in patients with Hodgkin's lymphoma undergoing allogeneic haematopoietic cell transplantation-a study by the Francophone Society of Bone Marrow Transplantation and Cellular Therapy. Bone Marrow Transplant. 2018;53(4):400-409.
47. Hsu J, Artz A, Mayer SA, et al. Combined haploidentical and umbilical cord blood allogeneic stem cell transplantation for high-risk lymphoma and chronic lymphoblastic leukemia. Biol Blood Marrow Transplant. 2018;24(2):359-365.

48. Kallam A, Armitage JO. Current and emerging treatment options for a patient with a second relapse of Hodgkin's lymphoma. Expert Rev Hematol. 2018;11(4):293-300.
49. Kanate AS, Kumar A, Dreger P, et al. Maintenance therapies for Hodgkin and non-Hodgkin lymphomas after autologous transplantation: A consensus project of ASBMT, CIBMTR, and the Lymphoma Working Party of EBMT. JAMA Oncol. 2019 Feb 28 [Epub ahead of print].
50. Karantanos T, Politikos I, Boussiotis VA. Advances in the pathophysiology and treatment of relapsed/refractory Hodgkin's lymphoma with an emphasis on targeted therapies and transplantation strategies. Blood Lymphat Cancer. 2017;7:37-52.
51. Marani C, Raiola AM et al. Haploidentical Transplants with Post-Transplant Cyclophosphamide for Relapsed or Refractory Hodgkin Lymphoma: The Role of Comorbidity Index and Pretransplant Positron Emission Tomography. Biol Blood Marrow Transplant. 2018 Dec;24(12):2501-2508.
52. Martínez C, Gayoso J et al. Post-Transplantation Cyclophosphamide-Based Haploidentical Transplantation as Alternative to Matched Sibling or Unrelated Donor Transplantation for Hodgkin Lymphoma: A Registry Study of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation. J Clin Oncol. 2017 Oct 20;35(30):3425-3432.
53. Mei M, Chen R. How to approach a Hodgkin lymphoma patient with relapse after autologous SCT: Allogeneic SCT. Clin Lymphoma Myeloma Leuk. 2018;18(1):26-33.
54. Moskowitz CH. Should all patients with HL who relapse after ASCT be considered for allogeneic SCT? A consult, yes; a transplant, not necessarily. Blood Adv. 2018;2(7):821-824.
55. Mottok A, Steidl C. Biology of classical Hodgkin lymphoma: Implications for prognosis and novel therapies. Blood. 2018;131(15):1654-1665.
56. Peggs KS. Should all patients with Hodgkin lymphoma who relapse after autologous SCT be considered for allogeneic SCT? Blood Adv. 2018;2(7):817-820.
57. Rashidi A, Ebadi M, Cashen AF. Allogeneic hematopoietic stem cell transplantation in Hodgkin lymphoma: a systematic review and meta-analysis. Bone Marrow Transplant. 2016 Apr;51(4):521-8. doi: 10.1038/bmt.2015.332. Epub 2016 Jan 4. PubMed PMID: 26726948.
58. Sibon D, Morschhauser F et al. Single or tandem autologous stem-cell transplantation for first-relapsed or refractory Hodgkin lymphoma: 10-year follow-up of the prospective H96 trial by the LYSA/SFGM-TC study group. Haematologica. 2016 Apr;101(4):474-81.
59. Smith EP, Li H, Friedberg JW, et al. Tandem autologous hematopoietic cell transplantation for patients with primary progressive or recurrent Hodgkin lymphoma: A SWOG and Blood and Marrow Transplant Clinical Trials Network Phase II Trial (SWOG S0410/BMT CTN 0703). Biol Blood Marrow Transplant. 2018;24(4):700-707.

Review/Revision History:
4/24/13: New Policy
6/2/15: Revised pretransplantation criteria
9/21/16: Policy reviewed and criteria was updated for both allo and auto stem cell transplants. Tandem HSCT are considered investigational (I/E) to treat patients with any stage, grade, or subtype of Hodgkin's and Non-Hodgkin's Lymphoma. Professional guidelines are reference sections were updated.
9/19/17 & 3/8/18: Policy reviewed, no changes.
12/10/2019: Policy reviewed and updated for allo and auto stem cell transplants. Removed age criteria for both Hodgkin and Non-Hodgkin transplants. Added that tandem allo transplants are I/E. Updated references and guidelines. Removed old studies from the summary of medical evidence section. Clarified that haploididentical transplants may be considered medically necessary when there are no matched sibling or unrelated donors for Hodgkin allogeneic transplants only.