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.

**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:
  - chronic smokers
  - > 50 years age
  - 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]
  - Karnofsky score 70-100%
  - Eastern Cooperative Oncology Group (ECOG) grade 0-2
- Neurological exam and clearance for transplant: [ONE]
  - Normal exam by H&P
  - 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:
  - *Complete blood count, Kidney profile (blood urea nitrogen, creatinine), electrolytes, calcium, phosphorous, albumin, liver function tests, Coagulation profile (prothrombin time, and partial thromboplastin time)*
  - *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
  o UDS (urine drug screen) if patient is current or gives a history of past drug abuse
  *Colonoscopy (if indicated or if patient is ≥50 years 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 years 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: 26-45

Non-Hodgkin’s Lymphoma 26 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
  * Age < 70 years
  * Classification of Lymphoma: [ONE]
    o Diffuse large B cell or High Grade lymphoma (DLBCL): 31 32 [ONE]
      ◇ First remission in intermediate high risk or high risk: Must have three risk factors for intermediate high-risk and > four of the following risk factors for high risk: 37
        ➢ Age > 60 years
        ➢ Advanced stage disease (III or IV)
        ➢ ECOG performance status 2-4
        ➢ Extranodal site involvement > 2
        ➢ Elevated serum lactate dehydrogenase
      ◇ Chemosensitive relapsed disease 37
      ◇ No complete remission with initial treatment
      ◇ Second or subsequent remission
    o Mantle cell: 40 [ALL]
      ◇ First remission following initial therapy
      ◇ Chemotherapy sensitive relapsed disease
    o Burkitt’s lymphoma: [ONE]
◊ First remission
◊ Relapsed disease in patients with chemosensitivity

○ Follicular. \(^3\,^1\,^2\) [ONE]
  ◊ Poor response to initial treatment
  ◊ Initial remission duration <12 months
  ◊ First relapse
  ◊ Transformation to diffuse large B-cell lymphoma \(^4\)

○ Other high risk lymphomas (Peripheral T cell lymphoma): \(^3\,^1\,^2\,^4\) [ONE]
  ◊ First complete remission with intermediate-high international prognostic index (IPI)
  ◊ Chemotherapy sensitive relapsed disease

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 or High Grade lymphoma (DLBCL) who are intermediate or high risk: \(^3\,^1\,^2\) [ONE]
    ◊ First remission in intermediate high risk or high risk: Must have three risk factors for intermediate high-risk and > four of the following risk factors for high risk: \(^3\,^7\)
      ➢ Age > 60 years
      ➢ Advanced stage disease (III or IV)
      ➢ ECOG performance status 2-4
      ➢ Extranodal site involvement > 2
      ➢ Elevated serum lactate dehydrogenase
    ◊ Chemosensitive relapsed disease \(^3\,^7\)
    ◊ No complete remission with initial treatment
    ◊ Second or subsequent remission

  - Burkitt’s lymphoma: [ONE]
    ◊ First remission in high risk category: [ONE]
      ➢ Elevated serum lactate dehydrogenase
      ➢ Abdominal involvement
    ◊ Relapsed disease in patients with [ONE]
      ➢ Chemosensitivity
      ➢ Post autologous stem cell transplant

  - Follicular: \(^3\,^1\,^2\) [ONE]
    ◊ Poor response to initial treatment
    ◊ Initial remission duration <12 months
First relapse
Transformed to diffuse large B-cell lymphoma

- Cutaneous T-cell Lymphoma (Mycosis Fungoides/Sezary Syndrome: [ONE]
  - Relapsed disease
  - Refractory disease
  - Progressive disease

- Adult T-cell Lymphoma:
  - After complete response for persistent or progressive disease

- Mantel cell: 37 [ALL]
  - Second remission following initial therapy

- Other high risk lymphomas: 31 32
  - Chemotherapy sensitive relapsed disease

**Hodgkin Lymphoma** 27-29 35 36 37 39 41

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
- Age < 70 years
- Therapeutic response to treatment: 37 [ONE]
  - Induction failure
  - Partial remission: no initial complete response
  - Relapsed disease defined as the reappearance of disease in sites of prior disease and/or in new sites after initial therapy and attainment of complete response: 39 [ONE]
    - Early relapse defined as < 12 months after treatment
    - Second relapse after treatment for first relapse
    - Generalized relapse > 12 months after treatment

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 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
- Reduced intensity stem cell transplant as salvage therapy; and
- Relapsed disease post autologous transplant
5. **Tandem autologous hematopoietic stem cell transplantation** is considered experimental, investigational and unproven due to insufficient evidence in the peer reviewed literature that has defined patient selection criteria and long term health outcomes. 46

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/m² 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.
- Tandem HSCT (e.g., autologous - autologous, autologous – allogeneic) is considered investigational to treat patients with any stage, grade, or subtype of Hodgkin’s and Non-Hodgkin’s Lymphoma.
- Allogeneic and Autologous HSCT as initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for Non-Hodgkin’s Lymphoma and Hodgkin Lymphoma is considered investigational.
- A repeat autologous or allogeneic (ablative or non-myeloablative) hematopoietic stem cell transplant due to persistent, progressive or relapsed Non-Hodgkin’s Lymphoma and Hodgkin Lymphoma is considered investigational.
- Hematopoietic stem cell collection, storage and freezing for a future unplanned transplant is not covered.

**Summary of Medical Evidence**

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. Additional relevant studies are outlined below.

**Non-Hodgkin Lymphoma**

*Hematopoietic Stem-Cell Transplant (HSCT)*

Ladetto et al. (2008) reported the results of a Phase III, randomized, multicenter trial of patients with high-risk follicular lymphoma, treated at diagnosis. A total of 134 patients were enrolled to receive either rituximab-supplemented high-dose chemotherapy (HDC) and autologous HSCT or six courses of cyclophosphamide,
doxorubicin (or Adriamycin®), vincristine (Oncovin®), and prednisolone (CHOP) followed by rituximab (CHOP-R). Of these patients 79% completed R-HDC and 71% completed CHOP-R. Complete remission was 85% with HSCT and 62% with CHOP-R. At a median follow-up of 51 months, the 4-year event-free survival (EFS) was 61% and 28% (HSCT vs. CHOP-R, respectively), with no difference in overall survival (OS). Molecular remission (defined as negative results by polymerase chain reaction on two or more consecutive bone marrow samples spaced 6 months apart in patients who reached complete remission [CR]) was achieved in 80% of HSCT and 44% of CHOP-R patients, and was the strongest independent outcome predictor. In 71% of the CHOP-R patients who had a relapse, salvage HSCT was performed and achieved an 85% CR rate and a 68% 3-year EFS. The authors concluded that there was no OS advantage to treating high-risk FL initially with HSCT, but that relapsed/refractory FL would be the most appropriate setting for this therapy. 

In 2006, Sebban et al. reported the results of a randomized, multicenter study. A total of 209 patients received cyclophosphamide, Adriamycin, etoposide, prednisolone (CHVP) plus interferon (CHVP-I arm) and 131 patients received CHOP followed by high-dose chemotherapy (HDC) with total body irradiation and autologous HSCT. Response rates were similar in both groups (79% and 78% after induction therapy, respectively). After a median follow-up of 7.5 years, intent-to-treat analysis showed no difference between the two arms for OS (p=0.53) or EFS (p=0.11). The authors concluded that there was no statistically significant benefit to first-line, high-dose therapy in patients with follicular lymphoma, and that high-dose therapy should be reserved for relapsing patients.

Deconinck and colleagues investigated the role of autologous HSCT as initial therapy in 172 patients with follicular lymphoma considered at high risk due to the presence of either B symptoms (i.e., weight loss, fever, or night sweats), a single lymph node larger than 7 cm, more than 3 involved nodal sites, massive splenomegaly, or a variety of other indicators of high tumor burden. The patients were randomized to receive either an immunochemotherapy regimen or a high-dose therapy followed by purged autologous HSCT. While the autologous HSCT group had a higher response rate and longer median EFS, there was no significant improvement in OS rate due to an excess of secondary malignancies. The authors concluded that autologous HSCT cannot be recommended as the standard first-line treatment of follicular lymphoma with a high tumor burden.

Lenz and colleagues (2004) reported on the results of a trial of 307 patients with advanced stage lymphoma in first remission, including follicular lymphoma, mantle cell lymphoma, or lymphoplasmacytoid lymphoma. Patients were randomized to receive either consolidative therapy with autologous HSCT or interferon therapy. The 5-year progression-free survival (PFS) rate was considerably higher in the autologous HSCT arm (64.7%) compared to the interferon arm (33.3%). However, the median follow-up of patients is still too short to allow any comparison of OS.

Betticher et al. (2006) reported the results of a Phase III multicenter, randomized trial (MISTRAL) comparing sequential HDC with autologous HSCT with standard CHOP as first-line therapy in 129 patients with aggressive NHL. Remission rates were similar in the two groups, and after a median observation time of 48 months, there was no difference in OS with 46% in the sequential autologous HSCT group and 53% in the group that received CHOP (p=0.48). The authors concluded that sequential autologous HSCT did not confer any survival benefit as initial therapy in patients with aggressive NHL.
Monjanel and colleagues (2010) published a pilot phase II trial by the French Groupe Ouest-Est des Leucémies et Autres Maladies du Sang (GOELAMS) evaluating tandem HDT with PBSC support in a series of 45 patients with aa-IPI equal to 3 untreated aggressive non-Hodgkin's lymphoma. After induction with an anthracyclin-containing regimen, responders underwent tandem HDT conditioned by high-dose mitoxantrone plus cytarabine for the first HDT and total-body irradiation (TBI), carmustine, etoposide, and cyclophosphamide for the second HDT. Thirty-one patients out of 41 evaluable patients completed the program. There were 4 toxic deaths. The complete response rate was 49%. With a median follow-up of 114 months for surviving patients, the OS was 51%, and 19 out of the 22 patients (86%) who reached a complete response are alive and relapse-free. Recent prospective evaluation of quality of life and comorbidities of surviving patients does not reveal long-term toxicities of the procedure. In the era of monoclonal antibodies and response-adapted therapy, the role of tandem HDT still need to be determined.

**Hodgkin’s Lymphoma**

**Hematopoietic Stem-Cell Transplant (HSCT)**

A 2012 comparative effectiveness review by the Agency for Healthcare Research and Quality (AHRQ) considered the use of autologous HSCT in pediatric patients with relapsed or refractory disease. Based upon available evidence (small, retrospective case series), the researchers concluded that, “Overall there appears to be a favorable risk-benefit profile for the treatment of Hodgkin’s disease with HSCT in patients with progressive disease or relapse” and that among patients for whom autologous transplant is not an option, allogeneic transplant should be considered.

The British National Lymphoma Investigation (BNLI) study was the first to show a progression-free survival benefit with autologous HSCT over conventional chemotherapy in relapsed or refractory HL patients. Forty patients with relapsed or refractory HL were given chemotherapy without transplant (n=20) or autologous transplant after HDC (n=20).[14] A significantly better event-free survival (EFS) at 3 years of 53% versus 10% was reported in the patients who underwent transplant versus the group that did not.

A larger trial by the German Hodgkin Study Group (GHSG) and European Group for Blood and Marrow Transplantation (EBMT) confirmed the findings from the BNLI study. Patients relapsing after initial chemotherapy were randomized to chemotherapy without transplant or to autologous HSCT. In the final analysis of 144 patients, freedom from treatment failure at 3 years was 55% in the transplanted group versus 34% in the nontransplanted group. This benefit was maintained in subgroup analysis, regardless of early or late relapse and the results were confirmed in follow-up data at 7 years.

The European Group for Blood and Marrow Transplantation (EBMT) in 2008 published the results of the outcomes of 89 HL patients with relapsed or refractory disease who received a RIC allogeneic HSCT and were compared to 79 patients who received myeloablative conditioning. Sixty-two percent of the RIC-group had undergone a previous autologous HSCT versus 41% of the patients in the myeloablative group. Although the incidence of relapse was nearly double in the RIC group (57% vs. 30%), after a median follow-up for surviving patients of 75 months (range, 12 to 120 months), 24 in the RIC group (26.9%) and 18 in the conventional group (22.8%) were alive. Five-year OS was 22% (95% CI: 13–31%) for the conventional group and 28% (95% CI: 23–33%) for the RIC group. This benefit was maintained in subgroup analysis, regardless of early or late relapse.
Independent adverse prognostic factors for OS were a previously failed autologous HSCT (RR=1.59; 95% CI: 1.07 to 2.35; p=0.02), the use of myeloablative conditioning (RR=1.62; 95% CI: 1.27 to 3.29; p=0.04), and the presence of refractory disease (RR=1.51; 95% CI: 1.03–2.21; p=.003).

Sarina and colleagues (2010) reported a retrospective study of 185 patients with HL who had failed an autologous HSCT. One hundred twenty-two had donors available for a salvage RIC allogeneic HSCT; of these, 104 (85%) were transplanted. Sixty-three patients did not have a suitable donor and were treated with salvage chemotherapy or radiotherapy. Clinical characteristics between the two groups did not differ. After a median follow-up of 48 months, PFS and OS were better in the group that underwent the salvage allogeneic HSCT (39.3% vs. 14.2% and 66% vs. 42%, respectively; p<0.001), showing a survival benefit of an RIC allogeneic HSCT versus conventional treatment after a failed autologous HSCT for HL. This study supports one of the policy statements for RIC HSCT.

Tandem Transplant

Morschhauser and colleagues (2008) reported on the results of a multicenter prospective trial that evaluated a risk-adapted salvage treatment with single or tandem autologous HSCT in 245 patients with relapsed/refractory HL. Median follow-up time was 51 months (range: 20–110 months). Patients were categorized as poor risk (n=150) if they had primary refractory disease (n=77) or two or more of the following risk factors at first relapse: time to relapse less than 12 months, stage III or IV disease at the time of relapse, or relapse occurring within previously irradiated sites (n=73). Poor risk patients were eligible for tandem autologous transplants. Intermediate-risk patients (n=95), defined as one risk factor at relapse, were eligible for a single transplant. Overall, 70% of the poor-risk patients received tandem transplants and 97% of the intermediate-risk patients received a single transplant.

Fung and colleagues (2007) reported results from a pilot study to evaluate the toxicities and efficacy of tandem autologous HSCT in patients with primary refractory or poor risk recurrent HL. The study involved 28 patients with primary progressive and 18 with recurrent HL who were enrolled into the study between April 1998 and March 2000. Patients had at least one of the following poor prognostic factors: first complete remission less than 12 months, extranodal disease, or B symptoms at relapse. Forty-one patients (89%) received the second transplant. With a median follow-up of 5.3 years (1.6–8.1), the 5-year OS and PFS were 54% (95% CI: 40–69%) and 49% (95% CI: 34–63%), respectively.

Castagna and colleagues (2007) conducted a prospective study to evaluate the feasibility and efficacy of tandem high-dose chemotherapy (HDCT) in the treatment of refractory or relapsed Hodgkin's lymphoma (HL). Thirty-two patients were treated with salvage chemotherapy (IGEV, ifosfamide, gemcitabine, and vinorelbine) and chemo-sensitive patients received a first HDCT course with melphalan 200 mg/m(2) (MEL200) and a second BEAM course. The median time interval between the two HDCT courses was 66 days. The median number of reinfused CD34(+) cells was 4.7 x 10(6)/kg after MEL200 and 5.8 x 10(6)/kg after BEAM. The hematological reconstitution after both HDCT courses did not differ. No grade III or IV renal, hepatic, lung, cardiac, and neurological toxicity was observed. Severe (grade III and IV) oral mucositis was the most prominent complication affecting 60 and 50% of patients after MEL200 and BEAM, respectively. Fever of unknown origin occurred in 65 and 70% of patients after MEL200 and BEAM, respectively. One patient died from septic shock during the aplasia period following BEAM. In an intention-to-treat analysis, the overall response rate
increased after each stage of protocol, ranging from 47% to 65% and 75% after IGEV, MEL200, and BEAM, respectively. The authors concluded that tandem HDCT is feasible and effective in patients with relapsed or refractory HL.  

Cochrane 26-29

A 2013 review by Rancea at al. suggests a PFS benefit for patients with relapsed or refractory HL after first-line therapy, who are treated with HDCT followed by ASCT compared to patients treated with conventional chemotherapy. In addition, data shows a positive trend regarding OS, but more trials are needed to detect a significant effect.

A 2012 review by Schaaf and colleagues concluded that there is no evidence to support the use of HSCT for improved overall survival in first-line treatment of FL. Although improvements in treatment-related mortality and secondary malignancies were similarly not significantly associated with use of HSCT, transplantation was significantly associated with improved progression-free survival in FL.

A 2008 review by Greb et al. suggested that autologous HSCT did not have an effect on OS when compared with conventional chemotherapy. According to the IPI, subgroup analysis of prognostic groups showed no survival differences between autologous HSCT and conventional chemotherapy in 12 trials, and EFS also was not significantly different between the two groups. The authors concluded that despite higher CR rates, there is no benefit for autologous HSCT as first-line treatment in aggressive NHL.

Professional Organizations

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

- **Follicular:**
  - Poor response to initial treatment
  - Initial remission duration <12 months
  - First relapse
  - Transformation to diffuse large B-cell lymphoma

- **Diffuse Large B-Cell or High-Grade Lymphoma**
  - At first or subsequent relapse
  - CR1 for patients with high or high-intermediate IPI risk
  - No CR with initial treatment
  - Second or subsequent remission

- **Mantle Cell**
  - After initiation of therapy

- **Other High-Risk Lymphomas**
  - After initiation of therapy
**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.

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<tr>
<td>38209</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing</td>
</tr>
<tr>
<td>38210</td>
<td>Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion</td>
</tr>
<tr>
<td>38211</td>
<td>Transplant preparation of hematopoietic progenitor cells; tumor cell depletion</td>
</tr>
<tr>
<td>38212</td>
<td>Transplant preparation of hematopoietic progenitor cells; red blood cell removal</td>
</tr>
<tr>
<td>38213</td>
<td>Transplant preparation of hematopoietic progenitor cells; platelet depletion</td>
</tr>
<tr>
<td>38214</td>
<td>Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion</td>
</tr>
<tr>
<td>38215</td>
<td>Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer</td>
</tr>
<tr>
<td></td>
<td><strong>Cell infusion codes</strong></td>
</tr>
<tr>
<td>38240</td>
<td>Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic</td>
</tr>
<tr>
<td>38241</td>
<td>Bone marrow or blood-derived peripheral stem cell transplantation; autologous</td>
</tr>
<tr>
<td>38242</td>
<td>Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions</td>
</tr>
<tr>
<td>38243</td>
<td>Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic hematopoietic cellular transplant boost</td>
</tr>
<tr>
<td></td>
<td><strong>HCPCS</strong></td>
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<tr>
<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
</tr>
<tr>
<td>S2142</td>
<td>Cord blood derived stem-cell transplantation, allogeneic</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td></td>
<td><strong>ICD-9</strong></td>
</tr>
<tr>
<td>200.00-200.08</td>
<td>Lymphosarcoma and reticulosarcoma</td>
</tr>
<tr>
<td>ICD-10</td>
<td>Description</td>
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<tr>
<td>C81.70- C81.79</td>
<td>Other classical Hodgkin lymphoma</td>
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<tr>
<td>C82.0-C82.99</td>
<td>Follicular Lymphoma</td>
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<tr>
<td>C83.1-C83.19</td>
<td>Mantle cell lymphoma, unspecified site</td>
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<tr>
<td>C83.30-C83.39</td>
<td>Diffuse large B-cell lymphoma</td>
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<td>C83.50-C83.59</td>
<td>Lymphoblastic (diffuse) lymphoma</td>
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<tr>
<td>C83.70-C83.79</td>
<td>Burkitt lymphoma, unspecified site</td>
</tr>
<tr>
<td>C85.1-C85.99</td>
<td>Other types on non-Hodgkin lymphoma</td>
</tr>
</tbody>
</table>

**Resource References**

**Government Agency**

**Peer Reviewed Publications**

**Cochrane Reviews**


**Professional Society Guidelines**

34. The American Society for Blood and Marrow Transplantation (ASBMT) Position Statement:
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36. National Comprehensive Cancer Network (NCCN) [Website]:

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42. UpToDate: Freedman AS, Friedberg JW:
   - Hematopoietic cell transplantation in follicular lymphoma. 2016.
   - Treatment of relapsed or refractory diffuse large B cell lymphoma. 2016.
43. UpToDate: Jacobsen E, Freedman AS. Treatment of relapsed or refractory peripheral T cell lymphoma. 2016
44. UpToDate: Hoppe RT, Kim YH. Treatment of advanced stage (IIB to IV) mycosis fungoides and Szary syndrome. 2016.
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