**PREFACE**

This Medical Guidance 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 exclusions 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 following website: [http://www.cms.hhs.gov/center/coverage.asp](http://www.cms.hhs.gov/center/coverage.asp).

**FDA INDICATIONS**

Stem cell transplantation is a procedure that is not subject to FDA regulation.

**CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)**

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 medical coverage guidance (MCG) document and provide the directive for all Medicare members. The directives from this MCG document may be followed if there are no available NCD or LCD documents available and outlined below.

CMS does have a NCD called Stem Cell Transplantation (110.8.1)\(^1\) and covers autologous stem cell transplantation (AuSCT) for resistant non-Hodgkin’s lymphomas or those presenting with poor prognostic features following an initial response and for advanced Hodgkin’s disease who have failed conventional therapy and have no HLA-matched donor.

CMS indicates that bone marrow and peripheral blood stem cell transplantation is a process which includes mobilization, harvesting, and transplant of bone marrow or peripheral blood stem cells and the administration of high dose chemotherapy or radiotherapy prior to the actual transplant. When bone marrow or peripheral blood stem cell transplantation is covered, all necessary steps are included in coverage. When bone marrow or peripheral blood stem cell transplantation is non-covered, none of the steps are covered.
INITIAL COVERAGE CRITERIA

All transplants must be approved by the Medical Director prior to authorization

Members must meet the criteria outlined below for transplantation and the diagnosis must be made by a Hematologist, Oncologist and/or transplant surgeon.

Pre-Transplant Evaluation:

1. General requirements for transplant evaluation include all of the following:
   - History and physical examination
   - Psychosocial evaluation and clearance: This must be completed and documentation submitted for review before any additional transplant work-up or testing is initiated.
   - Dietary consult and clearance for transplant
   - Disease evaluation may include all the following:
     - Bone marrow biopsy and/or bone marrow aspiration: must show adequate response to therapy
     - CT scan
     - PET scan
   - Cardiac Echocardiogram: Ejection fraction > 50%
   - EKG
   - Chest X-ray
   - Performance Status: [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
   - Pulmonary function testing: [ALL]
     - diffusion capacity (DLCO) >60%
     - forced expiratory volume (FEV) >60%
     - forced capacity (FVC) >60%
   - Lab studies:
     - Complete blood cell count, liver function tests, kidney profile, coagulation profile (prothrombin time, partial thromboplastin time)
       - SGOT or SGPT >2x upper limit of normal
     - HIV testing
     - Hepatitis A (HAV), Hepatitis B (HBV), Hepatitis C (HCV), Hepatitis D, Ebstein-Barr virus (EBV), cytomegalovirus (CMV) serology, syphilis, toxoplasmosis, herpes simplex virus
Within the last 12 months the following is required:

- Colonoscopy (indicated > age 50 with removal of any polyps if applicable)
- Dental examination (contact plan for coverage criteria)
- GYN examination with Pap smear (indicated > age 18) with complete workup and treatment of abnormal results as indicated
- Mammogram (indicated > age 40) with complete workup and treatment of abnormal results as indicated
- Osteoporosis screening with DEXA scan: [ONE]
  - cholestatic disorders
  - prolonged corticosteroid therapy
  - postmenopausal women
  - age > 65

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<tr>
<td>Able to carry on normal activity, no evidence of disease</td>
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<tr>
<td>Able to carry on normal activity, minor signs or symptoms of disease</td>
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<tr>
<td>Normal activity with effort, some signs and symptoms of disease</td>
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<tr>
<td>Cares for self, unable to carry on normal activity or to work</td>
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<tr>
<td>Requires occasional assistance from others but able to care for most needs</td>
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<tr>
<td>Requires considerable assistance from others and frequent medical care</td>
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<tr>
<td>Disabled, requires special care and assistance</td>
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<tr>
<td>Severely disabled, hospitalization indicated, death not imminent</td>
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<tr>
<td>Very sick, hospitalization indicated, active support treatment necessary</td>
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<tbody>
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<tr>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
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<tr>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of</td>
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<td>waking hours</td>
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<tr>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair</td>
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**Criteria for Transplantation:**

**Non-Hodgkin’s Lymphoma**

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 \(^2\,^6\,^33\):

- **Age < 70 years**
- **Classification of Lymphoma:** [ONE]
  - Diffuse large B cell or High Grade lymphoma (DLBCL)\(^2\,^6\,^26\): [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
      - Age > 60 years
      - Advanced stage disease (III or IV)
      - ECOG performance status 2-4
      - Extranodal site involvement > 2
      - Elevated serum lactate dehydrogenase
    - Relapsed disease
  - Mantel cell \(^2\,^6\,^27\): [ALL]
    - First remission following initial therapy
  - Burkitt’s lymphoma \(^2\,^8\,^6\,^28\): [ONE]
    - First remission
    - Relapsed disease in patients with chemosensitivity
  - Follicular \(^2\,^6\,^25\): [ONE]
    - Poor response to initial treatment
    - Initial remission duration <12 months
    - Second relapse
    - Transformation to diffuse large B-cell lymphoma
  - Peripheral T Cell Lymphoma \(^2\,^22\,^49\): [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 \(^14\) (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:

- Classification of Lymphoma: [ONE]
  - Diffuse large B cell or High Grade lymphoma (DLBCL): [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
      - Age > 60 years
      - Advanced stage disease (III or IV)
      - ECOG performance status 2-4
      - Extranodal site involvement > 2
      - Elevated serum lactate dehydrogenase
    - Relapsed disease
  
  - 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: [ONE]
    - Poor response to initial treatment
    - Initial remission duration <12 months
    - Second relapse
    - Transformation 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

  - Peripheral T Cell Lymphoma
Chemotherapy sensitive relapsed disease

Donor lymphocyte infusion (DLI):

3. *Donor lymphocyte infusion (DLI), collection and cryopreservation* may be authorized following a medically necessary allogeneic hematopoietic stem cell transplant:

- For incomplete chimerism and disease relapse in the setting of incomplete chimerism (defined as incomplete donor stem cell grafting in the recipient's bone marrow); and
- Donor lymphocytes must be collected from the original hematopoietic stem cell donor

Hodgkin Lymphoma

4. *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:

- Age < 70 years
- Therapeutic response to treatment: [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: [ONE]
    - Early relapse defines as < 12 months after treatment
    - Second relapse after treatment for first relapse
    - Generalized relapse > 12 months after treatment

5. *Tandem autologous (autologous/autologous) hematopoietic stem cell transplantation* may be authorized as a risk-adapted salvage treatment for:

- For primary refractive Hodgkin disease defined as: [ONE]
  - Disease regression of less than 50% after four to six cycles of anthracycline-containing chemotherapy
  - Disease progression during induction therapy
  - Disease progression within 90 days after the completion of first-line treatment

- For relapse after standard therapy defined as [Two]:

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- Time to relapse less than 12 months
- Stage III or IV at relapse
- Relapse within previously irradiated site

### Continuation of Therapy

A review for any stem cell transplantation procedure is valid for one year from the time the request was approved. Due to potential lengthy organ donor waiting time, an annual review of clinical information should be conducted to evaluate any changes in the member’s clinical status.

### 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 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.
- The following absolute contraindications to stem cell transplantation are not covered:
  - Active alcohol and/or other substance abuse including smoking (to remove as a contraindication there must be 6 months of documented abstinence through participation in a structured alcohol/substance abuse program with regular meeting attendance and negative random drug testing)
  - Documented history of non-compliance or inability to follow through with medication adherence or office follow-up
  - Irreversible brain damage or active central nervous system disease
  - Significant or advanced heart, lung, liver, kidney, gastrointestinal or other systemic or multi-system disease that is likely to contribute to a poor outcome after transplantation
  - No behavioral health disorder by history or psychosocial issues: [One]
    - 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

*Note*: Patient’s need to understand the importance of adherence to medication schedules and follow-up appointments/noncompliance is a major cause of graft failure.

- No adequate social/family support
Relative contraindications to stem cell transplantation include all of the following:  
- poor cardiac function (ejection fraction < 50%)
- poor liver function (bilirubin > 2.0mg/dl and transaminases greater than two times normal), unless related to AML
- poor renal function (creatinine clearance < 60ml/min)
- poor pulmonary function [diffusion capacity (DLCO) < 60% of predicted]
- active central nervous system involvement
- presence of human immunodeficiency virus (HIV)
- an active infection with any ONE of the following:
  - hepatitis B virus (HBV)
  - hepatitis C virus (HCV)
  - human T-cell lymphotropic virus (HTLV)-1
- Karnofsky rating <70% ; OR
- Eastern Cooperative Oncology Group (ECOG) performance status >2

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. 48

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 form 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. 9 10

**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.

**Donor Lymphocyte Infusion**

Following an allogeneic hematopoietic stem cell transplant, donor lymphocyte infusion is a form of adoptive immunotherapy and may be requested to induce a graft versus leukemia, or graft versus tumor, response without requiring the recipient to undergo additional high-dose chemotherapy. Donor lymphocytes are collected from the original donor through leukapheresis. This collection is an outpatient procedure for the donor. The lymphocytes are then either infused via vein into the recipient or are frozen for a more clinically appropriate time. 31 32

**Pretransplant Evaluation**

The goal of the pretransplant evaluation is to assess the ability of a patient to tolerate the surgery, post-operative immunosuppression, and transplant care. An extensive cardiopulmonary evaluation, screening for occult infection or cancer, and psychosocial evaluation is standard. Specific testing varies depending upon the patient's age, medical history, and transplant center practice. In addition, while a certain battery of tests may initiate the
work up, more testing may be indicated depending upon the condition of the patient or the initial test results. In addition to a standard medical evaluation the initial assessment should include a psychological and social support evaluation to identify issues that may impair a successful outcome after transplantation. These include a lack of information about the nature of the transplant procedure and post-transplant care, drug or alcohol dependence, compliance with complex medical and behavior regimens. The assessment includes education of the family and the support network of the patient because compliance with complex medical and behavior treatment is critical after any organ transplant procedure. Recipients must be able to incorporate complicated medications, follow-up appointments, and frequent laboratory visits into their schedules. Having an adequate support network aware of these requirements will encourage patient compliance and long-term success.  

**GENERAL INFORMATION**

Summary of Medical Evidence

**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. 32

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.[20] 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. 34

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. 36

*Allotransplant after a Failed Autotransplant*

There are currently no prospective randomized controlled studies comparing allotransplants to alternative strategies for managing failure (progression or relapse) after an autologous HSCT for NHL.

*Tandem Transplant*

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. 45
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.\(^{37}\)

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.\(^{38,39}\)

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.\(^{40,41}\)

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: 18–38%) for the RIC group. 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).\(^{42}\)

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.\(^{43}\)

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. 44

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. 46

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. 47

Hayes, Cochrane, UpToDate, MD Consult etc.

Hayes does not have a current technology directory report regarding stem cell transplantation for Hodgkin’s or Non-Hodgkin’s Lymphoma. Both of these reports are outdated and were archived.

Cochrane
Schaaf and colleagues\textsuperscript{29} conducted a systematic review and meta-analysis on the use of HSCT for as treatment of follicular lymphoma (FL) for the Cochrane databases, published in 2012. The researchers identified four trials focusing on HSCT as first-line treatment for FL and the primary outcome of the analysis was overall survival, and secondary outcomes included progression-free survival, treatment-related mortality, and secondary malignancies. After pooling results from the below trials, the authors 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.

Greb et al. undertook a systematic review and meta-analysis to determine whether HDC with autologous HSCT as first-line treatment in patients with aggressive NHL improves survival compared to patients treated with conventional chemotherapy, published in 2008. Fifteen randomized controlled trials (RCTs) including 3,079 patients were eligible for the meta-analysis. Thirteen studies with 2,018 patients showed significantly higher CR rates in the autologous HSCT group (p=0.004). However, 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.\textsuperscript{35}

UpToDate:

In a report called Hematopoietic cell transplantation in classical Hodgkin lymphoma\textsuperscript{3} the following key points are summarized:

- High dose chemotherapy and autologous hematopoietic cell transplantation (HCT) is considered the treatment of choice for the following subsets of patients:
  - Early relapse (less than 12 months after treatment) or induction failure
  - Second relapse after conventional treatment for first relapse
  - Generalized systemic relapse even beyond 12 months

- The use of autologous HCT in high risk patients with advanced disease in first remission is controversial and investigational.

- Autologous peripheral blood stem cells are the donor cells of choice because of more rapid hematologic recovery and shortened hospital stay when compared with autologous bone marrow transplantation

In a report called Hematopoietic cell transplantation (HCT) in follicular lymphoma\textsuperscript{25} the following key points are summarized: HCT is reserved for patients with relapsed or refractory follicular lymphoma or for those with histologic transformation to a more aggressive histology. Among patients with relapsed follicular lymphoma, a choice between HCT and chemotherapy without HCT is made on an individual basis. HCT is generally preferred for patients with clinically aggressive disease as demonstrated by a short remission duration. This is primarily based upon prospective randomized trials that have demonstrated a survival benefit from HCT in patients with relapsed follicular lymphoma, but failed to demonstrate a survival benefit in patients with
previously untreated disease. HCT is also a reasonable treatment option for select patients with follicular lymphoma that has transformed to a more aggressive non-Hodgkin lymphoma subtype.

In most centers in the United States, patients with one or more of the following factors are NOT considered eligible for autologous HCT:

- Direct bilirubin >2.0 mg/dL (34.2 µmol/liter)
- Serum creatinine >2.5 mg/dL (221 µmol/liter) unless on chronic stable dialysis
- Eastern Cooperative Oncology Group (ECOG) performance status 3 or 4 unless due to bone pain
- New York Heart Association functional status Class III or IV

In a report called Treatment of relapsed or refractory diffuse large B cell lymphoma(DLBCL)²⁶ the following key points are summarized:

- For patients with relapsed or refractory DLBCL that responds to second-line chemotherapy, high dose chemotherapy followed by autologous hematopoietic cell transplantation (HCT) results in superior survival rates than chemotherapy alone.
- Patients with chemotherapy-sensitive relapse, or who have chemotherapy-sensitive disease but have never achieved complete remission, have a 30 to 60 percent probability of disease-free survival (DFS) at three to five years and in comparison, patients with DLBCL resistant to second-line chemotherapy have a DFS of less than 10 to 20 percent even with autologous HCT.

Allogeneic hematopoietic cell transplantation (HCT) offers two potential benefits over autologous HCT, including a tumor-free source of stem cells and a possible graft-versus-tumor effect. Numerous non-controlled studies have investigated its use for patients with relapsed and refractory DLBCL. However, allogeneic HCT with a myeloablative chemotherapy regimen is associated with higher transplant-related morbidity and mortality resulting in similar rates of progression-free survival when compared with autologous HCT. Allogeneic HCT may be considered in patients with mobilization failure or relapse following an autologous HCT.

Professional Organizations

The National Cancer Institute (NCI) 2012⁹¹⁰⁴⁸:

Adult treatment options for Hodgkin disease include:

- For advanced, unfavorable Hodgkin disease (HD) in adults there is controversy 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 who relapse after initial combination chemotherapy these patients usually undergo reinduction with the same or another chemotherapy regimen followed by high-dose chemotherapy and autologous bone marrow or peripheral stem cell or allogeneic bone marrow rescue, which may result in a three- to four-year DFS rate of 27% to 48%.
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.

Children and adolescent treatment options with Hodgkin disease include:
- For children and adolescents with primary progressive/recurrent HD myeloablative chemotherapy with autologous HCT is the recommended approach for patients who develop refractory disease during therapy or relapsed disease within 1 year after completing therapy
- Autologous HCT has been preferred for patients with relapsed Hodgkin lymphoma because of the historically high transplant-related mortality (TRM) associated with allogeneic transplantation
- Following autologous HCT, the projected survival rate is 45% to 70% and progression-free survival is 30% to 89%
- Allogeneic HSCT for children with primary refractory/recurrent HD has been used with encouraging results for patients who fail following autologous HCT or for patients with chemoresistant disease

Adult treatment options for Non-Hodgkin disease include:
- Autologous or allogeneic bone marrow transplantation (BMT) or hematopoietic stem-cell transplantation (HSCT), is under clinical investigation for the treatment of indolent, noncontiguous stage II/III/IV non-Hodgkin lymphoma (NHL) in adults.
- Autologous or allogeneic HSCT are also noted to be under clinical evaluation for the treatment of patients at high risk of relapse with aggressive, noncontiguous stage II/II/IV adult NHL.

Children and adolescent treatment options for Non-Hodgkin disease include:
- Allogeneic and autologous bone marrow transplantations are noted to be treatment options for recurrent childhood Burkitt lymphoma, lymphoblastic lymphoma and anaplastic large-cell lymphoma (ALCL) types.

The American Society for Blood and Marrow Transplantation (ASBMT)
The 2011 Position statement indicates the following recommendations for the treatment of large B cell lymphoma:
- Autologous SCT provides a significant survival benefit and is recommended as part of salvage therapy for patients with chemo-sensitive relapsed DLBCL.
- Autologous SCT is not recommended for patients who achieve only a partial response to an abbreviated (3 cycles) induction regimen
- Autologous SCT as first-line therapy is not recommended for any International Prognostic Index group
- Planned tandem, or multiple sequential autologous SCTs are not recommended
- No upper age limit has been defined however, older age > 60 years is not a contraindication for autologous SCT as long as other SCT eligibility criteria are met.
- Survival outcomes after autologous and allogeneic SCT are equivalent and either donor option is recommended but they have competing risks with regard to relapse and transplant related mortality
- The data insufficient to recommend reduced intensity versus myeloablative conditioning for allogeneic SCT

The 2011 Position statement indicates the following recommendations for the treatment of follicular lymphoma:
- Autologous SCT as salvage therapy offers a statistically significant improvement in overall survival (OS) and progression-free survival (PFS)
- Autologous SCT is recommended for transformed FL
- Autologous SCT it is not recommended as first-line treatment for most patients because of no significant improvement in OS, a higher incidence of secondary myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML)
- There is no data regarding reduced intensity/nonmyeloablative allogeneic SCT versus autologous SCT. Comparison of these two techniques is biased by different patient selection criteria.

**The National Marrow Donor Program**[^2]: For Hodgkin lymphoma transplantation (HSCT) referral guidelines recommend referral for individuals who have no initial complete response to chemotherapy and for those in first or subsequent relapse. For 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
  - Second 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

- **Mantle Cell**
  - Following initial therapy

**National Comprehensive Cancer Network (NCCN):**

The 2012 guidelines for **Hodgkin’s Lymphoma** outline the following treatment recommendations[^21]:

- High-dose therapy/autologous stem-cell rescue is the best treatment option for patients with progressive or relapsed disease (category 2A recommendation).
- Allogeneic transplant is an option in select patients with progressive or relapsed disease (category 3 recommendation).

The 2012 guidelines for **Non-Hodgkin’s Lymphoma** outline the following treatment recommendations[^33]:

*Follicular lymphoma/Indolent lymphomas:*

[^2]: [Link to National Marrow Donor Program guidelines]
[^21]: [Link to NCCN guidelines for Hodgkin’s Lymphoma]
[^33]: [Link to NCCN guidelines for Non-Hodgkin’s Lymphoma]
- Autologous and allogeneic (fully myeloablative or nonmyeloablative) HSCT in (the latter in highly selected patients only) are recommended as consolidative therapy for patients in second or subsequent remission (category 2A recommendation).

**Diffuse large B-cell lymphoma:**

- Autologous HSCT is recommended as first-line consolidation only in high-risk patients, or in those enrolled in a clinical trial. (category 2B).
- Autologous HSCT is recommended for treatment of relapsed or refractory disease. (category 2A)

**Mantle cell lymphoma:**

- Autologous HSCT is recommended as first-line consolidative therapy. (category 2A)
- Autologous HSCT for patients with relapsed disease following CR to induction therapy, those patients who obtain only a PR to induction therapy, or those with progressive disease. (category 2A)
- Allogeneic (fully myeloablative or nonmyeloablative) for second-line consolidation. (category 2A)

**Peripheral T-cell lymphoma:**

- Autologous HSCT as first-line consolidation therapy in patients showing a good response to induction therapy (except those considered low-risk, e.g., ALCL ALK-positive). (category 2A)
- Autologous or allogeneic (fully myeloablative or nonmyeloablative) HSCT as second-line consolidation in patients with relapsed or refractory disease with PR or CR to second-line therapy. (category 2A)

**Cutaneous T-cell lymphoma (Mycosis Fungoides/Sezary Syndrome):**

- For relapsed, refractory, or progressive disease, consider allogeneic HSCT. (category 2A)

**Adult T-cell leukemia/lymphoma:**

- After CR or for persistent or progressive disease, consider allogeneic HSCT. (category 2A)

*Toronto (ON) Cancer Care Ontario Program Advisory Panel on Bone Marrow and Stem Cell Transplantation, and the Hematology Disease Site Group* 13: The 2009 Stem Cell Transplantation in Adults criteria outlines the following treatment recommendations:

- Hodgkin’s Lymphoma (HL): Autologous stem cell transplantation is the recommended treatment option for eligible chemosensitive patients with HL who are refractory to or who have relapsed after primary chemotherapy. Allogeneic stem cell transplantation is an option for chemosensitive patients with refractory or relapsed HL who are not candidates for autologous stem cell transplantation or who have a syngeneic (identical twin) donor. Stem cell transplantation is not recommended as part of primary therapy for HL.
The Non-Hodgkin’s Lymphomas:

- **Aggressive Histology NHL Including Diffuse Large B Cell Lymphoma and Aggressive T Cell Lymphomas (AH-NHL):** Autologous stem cell transplantation is the recommended option for eligible chemosensitive patients with AH-NHL refractory to or relapsed after primary therapy. Allogeneic stem cell transplantation is an option for eligible chemosensitive patients with refractory or relapsed AH-NHL who are not candidates for autologous stem cell transplantation or who have a syngeneic (identical twin) donor. Stem cell transplantation is not recommended for patients with AH-NHL as part of primary therapy.

- **Follicular Lymphoma (FL):** Autologous or allogeneic transplantation are options for selected patients with poor prognosis FL that progresses after second-line therapy.

- **Burkitt’s Lymphoma** Autologous and allogeneic transplantation are options for selected patients with Burkitt’s lymphoma beyond first remission. Stem cell transplantation is not recommended for patients with Burkitt’s lymphoma in first complete remission.

- **Mantle Cell Lymphoma (MCL) Autologous** stem cell transplantation is an option for eligible patients with MCL in first remission. Autologous or allogeneic transplantation are options for selected patients with MCL in second remission.

**CODING INFORMATION**

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**References**


49. UpToDate: Jacobsen E, Freedman AS. Treatment of relapsed or refractory peripheral T cell lymphoma. Waltham, MA, 2013. Dec 2012


51. Advanced Medical Review (AMR): Policy reviewed by MD board certified in Internal Medicine, Oncology and Hematology. March, 2013.