**Hematopoietic Stem-Cell Transplantation for Non-Hodgkin Lymphomas**

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The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. **Preauthorization is required and must be obtained through Case Management.** *Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

**Description**

**Hematopoietic Stem-Cell Transplantation**

Hematopoietic stem-cell transplantation (HSCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs, with or without whole-body radiation therapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II loci on chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

**Conventional Preparative Conditioning for HSCT**

The success of autologous HSCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient prior to undergoing bone marrow ablation. As a consequence, autologous HSCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

The conventional (“classical”) practice of allogeneic HSCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total-body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by nonself immunologic effector cells that develop after engraftment of allogeneic stem cells within the patient’s bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial...
adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone
marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic
HSCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases
susceptibility of the patient to opportunistic infections.

Reduced-Intensity Conditioning for Allogeneic HSCT

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of
cytotoxic drugs or radiation than are used in traditional full-dose myeloablative conditioning treatments. The
goal of RIC is to reduce disease burden but also to minimize as much as possible associated treatment-related
morbidty and nonrelapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic
transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed,
all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be
viewed as a continuum in effects, from nearly totally myeloablative to minimally myeloablative with
lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with
allogeneic HSCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will
subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to
eradicate residual malignant cells.

For the purposes of this Protocol, the term “reduced-intensity conditioning” will refer to all conditioning
regimens intended to be nonmyeloablative, as opposed to fully myeloablative (traditional) regimens.

Non-Hodgkin Lymphoma (NHL)

A heterogeneous group of lymphoproliferative malignancies, NHL usually originates in lymphoid tissue.
Historically, uniform treatment of patients with NHL was hampered by the lack of a uniform classification
system. In 1982, the Working Formulation (WF) was developed to unify different classification systems into one.
(1) The WF divided NHL into low-, intermediate-, and high-grade, with subgroups based on histologic cell type.
Since our understanding of NHL has improved, the diagnosis has become more sophisticated and includes the
incorporation of new immunophenotyping and genetic techniques. As a result, the WF has become outdated.

European and American pathologists proposed a new classification, the Revised European-American Lymphoma
(REAL) Classification (2) and an updated version of the REAL system, the new World Health Organization (WHO)
classification. (3) The WHO/REAL classification recognized three major categories of lymphoid malignancies
based on morphology and cell lineage: B-cell neoplasms, T-cell/natural killer (NK)-cell neoplasms, and Hodgkin
lymphoma.

The most recent lymphoma classification is the 2008 WHO classification:

Updated WHO Classification 2008 (4)

Mature B-cell neoplasms

• Chronic lymphocytic leukemia/small lymphocytic lymphoma
• B-cell prolymphocytic leukemia
• Splenic marginal zone lymphoma
• Hairy cell leukemia
• Splenic lymphoma/leukemia, unclassifiable
  o Splenic diffuse red pulp small B-cell lymphoma*
  o Hairy cell leukemia-variant*
• Lymphoplasmacytic lymphoma
  o Waldenstrom macroglobulinemia
• Heavy chain diseases
  o Alpha heavy chain disease
  o Gamma heavy chain disease
  o Mu heavy chain disease
• Plasma cell myeloma
• Solitary plasmacytoma of bone
• Extraosseous plasmacytoma
• Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
• Nodal marginal zone B-cell lymphoma (MZL)
  o *Pediatric type nodal MZL*
• Follicular lymphoma
  o *Pediatric type follicular lymphoma*
• Primary cutaneous follicle center lymphoma
• Mantle cell lymphoma
• Diffuse large B-cell lymphoma (DLBCL), not otherwise specified
  o T cell/histiocyte rich large B-cell lymphoma
  o *DLBCL associated with chronic inflammation*
  o *Epstein-Barr virus (EBV)+ DLBCL of the elderly*
• Lymphomatoid granulomatosis
• Primary mediastinal (thymic) large B-cell lymphoma
• Intravascular large B-cell lymphoma
• *Primary cutaneous DLBCL, leg type*
• ALK [anaplastic lymphoma kinase] + large B-cell lymphoma
• Plasmablastic lymphoma
• Primary effusion lymphoma
• *Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease*
• Burkitt lymphoma
• *B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma*
• B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

*These represent provisional entities or provisional subtypes of other neoplasms.

Diseases shown in *italics* are newly included in the 2008 WHO classification.

**Mature T-cell and NK-cell neoplasms**
• T-cell prolymphocytic leukemia
• T-cell large granular lymphocytic leukemia
• Chronic lymphoproliferative disorder of NK-cells*
• Aggressive NK-cell leukemia
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- **Systemic EBV** [Epstein-Bar virus] + T-cell lymphoproliferative disease of childhood (associated with chronic active EBV infection)
- **Hydroa vacciniforme-like lymphoma**
- Adult T-cell leukemia/ lymphoma
- Extranodal NK/T cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30+ T-cell lymphoproliferative disorder
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large-cell lymphoma
- **Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma**
- **Primary cutaneous gamma-delta T-cell lymphoma**
- **Primary cutaneous small/medium CD4+ T-cell lymphoma**
- Peripheral T-cell lymphoma, not otherwise specified
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma (ALCL), ALK+
- **Anaplastic large cell lymphoma (ALCL), ALK−**

*These represent provisional entities or provisional subtypes of other neoplasms.

Diseases shown in *italics* are newly included in the 2008 WHO classification.

In the U.S., B-cell lymphomas represent 80–85% of cases of NHL, and T-cell lymphomas represent 15–20%. NK (natural killer) lymphomas are relatively rare. (5)

The International Lymphoma Classification Project identified the most common NHL subtypes as follows: diffuse large B-cell lymphoma (DLBCL) 31%, follicular lymphoma (FL) 22%, small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL) 6%, mantle cell lymphoma (MCL) 6%, peripheral T-cell lymphoma (PTCL) 6%, and marginal zone B-cell lymphoma/mucosa-associated lymphoid tissue (MALT) lymphoma 5%. All other subtypes each represent less than 2% of cases of NHL. (5)

In general, the NHL can be divided into two prognostic groups, indolent and aggressive. Indolent NHL has a relatively good prognosis, with a median survival of 10 years; however, it is not curable in advanced clinical stages. (1) Early stage indolent NHL (stage 1 or 2) may be effectively treated with radiation alone. (1) Although indolent NHL is responsive to radiation and chemotherapy, a continuous rate of relapse is seen in advanced stages. (1) These patients can often be re-treated if their disease remains of the indolent type. Indolent NHL may transform into a more aggressive form, which is generally treated with regimens that are used for aggressive, recurrent NHL. Histologic transformation to higher grade lymphoma occurs in up to 70% of patients with low-grade lymphoma, (6) and median survival with conventional chemotherapy is one year or less.

FL (follicular lymphoma) is the most common indolent NHL (70–80% of cases), and often the terms indolent lymphoma and FL are used synonymously. Also included in the indolent NHL are SLL/CLL, lymphoplasmacytic lymphoma, marginal zone lymphomas, and cutaneous T-cell lymphoma.
Aggressive NHL has a shorter natural history; however, 30–60% of these patients can be cured with intensive combination chemotherapy regimens. (1) Aggressive lymphomas include DLBCL, MCL, PTCL, anaplastic large cell lymphoma, and Burkitt lymphoma.

Oncologists developed a clinical tool to aid in predicting the prognosis of patients with aggressive NHL (specifically DLBCL), referred to as the International Prognostic Index (IPI). (7) Prior to the development of IPI in 1993, prognosis was predominantly based on disease stage.

Based on the number of risk factors present and adjusted for patient age, the IPI defines four risk groups: low, low intermediate, high intermediate, and high risk, based on five significant risk factors prognostic of overall survival (OS):

1. Age older than 60 years
2. Elevated serum lactate dehydrogenase (LDH) level
3. Ann Arbor stage III or IV disease
4. Eastern Cooperative Oncology Group (ECOG) performance status of 2, 3, or 4
5. Involvement of more than one extranodal site.

Risk groups are stratified according to the number of adverse factors as follows: 0 or 1 is low risk, 2 is low intermediate, 3 is high intermediate, and 4 or 5 are high risk.

Patients with two or more risk factors have a less than 50% chance of relapse-free survival (RFS) and OS at five years. Age-adjusted (aaIPI) and stage-adjusted modifications of this IPI are used for younger patients with localized disease.

Adverse risk factors for age-adjusted IPI include stage III or IV disease, elevated LDH and ECOG performance status of two or greater and can be calculated as follows: 0 is low risk, 1 is low intermediate, 2 is high intermediate, and 3 is high risk.

With the success of the IPI, a separate prognostic index was developed for FL, which has multiple independent risk factors for relapse after a first complete remission. The proposed and validated Follicular Lymphoma International Prognostic Index (FLIPI) contains five adverse prognostic factors:

1. Age older than 60 years
2. Ann Arbor stage III–IV
3. Hemoglobin level less than 12.0 g/dL
4. More than four lymph node areas involved
5. Elevated serum lactate dehydrogenase (LDH) level.

These five factors are used to stratify patients into three categories of risk: low (0–1 risk factor), intermediate (2 risk factors), or poor (3 or more risk factors). (8)

Mantle Cell Lymphoma (MCL)

MCL comprises approximately 6–8% of NHL and has been recognized within the past 15 years as a unique lymphoma subtype with a particularly aggressive course. MCL is characterized by a chromosomal translocation t(11;14), and the term mantle cell lymphoma was proposed in 1992 by Banks et al. (9) The number of therapeutic trials are not as numerous for MCL as for other NHL, as it was not widely recognized until the REAL classification. MCL shows a strong predilection for elderly men, and the majority of cases (70%) present with disseminated (stage 4) disease and extranodal involvement is common. Localized MCL is quite rare. MCL has a median survival of approximately two to four years, and although most patients achieve remission with first-line
therapy, relapse inevitably occurs, often within 12–18 months. MCL is rarely, if ever, cured with conventional therapy, and no standardized therapeutic approach to MCL is used.

There had been no generally established prognostic index for patients with MCL. Application of the IPI or FLIPI system to patients with MCL showed limitations, which included no separation of some important risk groups. In addition, some of the individual IPI and FLIPI risk factors, including number of extranodal sites and number of involved nodal areas showed no prognostic relevance, and hemoglobin showed no independent prognostic relevance in patients with MCL. (10) Therefore, a new prognostic index for patients with MCL was developed and should prove useful in comparing clinical trial results for MCL.

MCL international prognostic index (MIPI):
1. Age
2. ECOG performance status
3. Serum LDH (calculated as a ratio of LDH to a laboratory’s upper limit of normal)
4. White blood cell count (WBC)
   - Zero points each are assigned for age younger than 50 years, ECOG performance 0–1, LDH ratio less than 0.67, WBC less than 6,700
   - One point each for age 50–59 years, LDH ratio 0.67–0.99, WBC 6,700–9,999
   - Two points each for age 60–69 years, ECOG 2–4, LDH ratio 1.00–1.49, WBC 10,000–14,999
   - Three points each for age 70 years or older, LDH ratio 1.5 or greater, WBC 15,000 or more.

MIPI allows separation of three groups with significantly different prognoses: (10)
- 0–3 points=low risk, 44% of patients, median OS not reached and a five-year OS rate of 60%
- 4–5 points=intermediate risk, 35% of patients, median OS 51 months
- 6–11 points=high risk, 21% of patients, median OS 29 months.

Peripheral T-Cell Lymphoma (PTCL)
The majority of peripheral T-cell lymphomas are aggressive and fall into the category of PTCL, unspecified (PTCL-u) or not otherwise specified (PTCL-NOS), angioimmunoblastic or anaplastic large cell which, combined make up approximately 60–70% of T-cell lymphomas. PTCLs are less responsive to standard chemotherapy than DLBCLs and carry a worse prognosis than aggressive B-cell counterparts. Survival rates at five years with standard chemotherapy regimens range from 20–35%. The poor results with conventional chemotherapy have prompted exploration of the role of HSCT as therapy.

Staging
The Ann Arbor staging classification is commonly used for the staging of lymphomas and is the scheme defined in the American Joint Committee on Cancer (AJCC) Manual for Staging Cancer. Originally developed for Hodgkin’s disease, this staging scheme was later expanded to include non-Hodgkin’s lymphoma.

Staging of Lymphoma: Ann Arbor Classification

Stage I
Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE).

Stage II
Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (IIIE).
Stage III
Involvement of lymph node regions on both sides of the diaphragm (III) which may also be accompanied by localized involvement of extralymphatic organ or site (IIIE) or by involvement of the spleen (IIIS) or both (IIISE).

Stage IV
Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement.

Related Protocols:
- Hematopoietic Stem-Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
- Hematopoietic Stem-Cell Transplantation for Hodgkin Lymphoma
- Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis
- Hematopoietic Stem-Cell Transplantation for Waldenstrom Macroglobulinemia

Corporate Medical Guideline
For patients with non-Hodgkin’s lymphoma (NHL) B-cell subtypes considered aggressive (except mantle cell lymphoma), either allogeneic hematopoietic stem-cell transplant (HSCT) using a myeloablative conditioning regimen or autologous HSCT may be considered medically necessary:
- as salvage therapy for patients who do not achieve a complete remission (CR) after first-line treatment (induction) with a full course of standard-dose chemotherapy;
- to achieve or consolidate a CR for those in a chemosensitive first or subsequent relapse; or
- to consolidate a first CR in patients with diffuse large B-cell lymphoma, with an age-adjusted International Prognostic Index score that predicts a high- or high-intermediate risk of relapse.

For patients with mantle cell lymphoma:
- Autologous HSCT may be considered medically necessary to consolidate a first remission.
- Allogeneic HSCT, myeloablative or reduced-intensity conditioning, may be considered medically necessary as salvage therapy.
- Autologous HSCT is considered investigative as salvage therapy.
- Allogeneic HSCT is considered investigative to consolidate a first remission.

For patients with NHL B-cell subtypes considered indolent, either allogeneic SCT using a myeloablative conditioning regimen or autologous HSCT may be considered medically necessary:
- as salvage therapy for patients who do not achieve CR after first-line treatment (induction) with a full course of standard-dose chemotherapy; or
- to achieve or consolidate CR for those in a first or subsequent chemosensitive relapse, whether or not their lymphoma has undergone transformation to a higher grade.

Reduced-intensity conditioning allogeneic HSCT may be considered medically necessary as a treatment of NHL in patients who meet criteria above for an allogeneic HSCT but who do not qualify for a myeloablative allogeneic HSCT (see Policy Guidelines).

Either autologous HSCT or allogeneic HSCT is considered investigative:
- as initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for any NHL;
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- to consolidate a first CR for patients with diffuse large B-cell lymphoma and an International Prognostic Index score that predicts a low- or low-intermediate risk of relapse;
- to consolidate a first CR for those with indolent NHL subtypes.

Tandem transplants are considered investigational to treat patients with any stage, grade, or subtype of NHL.

For patients with mature T-cell or NK-cell (peripheral T-cell) lymphoma:

- Autologous HSCT may be considered medically necessary to consolidate a first complete remission in high-risk subtypes. (see Policy Guidelines)
- Autologous or allogeneic HSCT (myeloablative or reduced-intensity conditioning) may be considered medically necessary as salvage therapy.
- Allogeneic HSCT is considered investigational to consolidate a first remission.

**Note:** Small lymphocytic lymphoma (SLL) may be considered a node-based variant of chronic lymphocytic leukemia (CLL). Therefore, SLL is considered in a separate Protocol. Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia is also considered in separate Protocol.

**Policy Guideline**

Reduced-intensity conditioning (RIC) would be considered an option in patients who meet criteria for an allogeneic stem-cell transplant (HSCT) but whose age (typically older than 55 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy) preclude use of a standard conditioning regimen.

In patients who qualify for a myeloablative allogeneic hematopoietic HSCT on the basis of overall health and disease status, allogeneic HSCT using either myeloablative or RIC may be considered. However, a myeloablative conditioning regimen with allogeneic HSCT may benefit younger patients with good performance status and minimal comorbidities more than allogeneic HSCT with RIC.

The term salvage therapy describes chemotherapy given to patients who have either: 1) failed to achieve complete remission after initial treatment for newly diagnosed lymphoma, or 2) relapsed after an initial complete remission.

A chemosensitive relapse is defined as relapsed non-Hodgkin lymphoma (NHL) that does not progress during or immediately after standard-dose induction chemotherapy (i.e., achieves stable disease or a partial response).

Transformation describes a lymphoma whose histologic pattern has evolved to a higher-grade lymphoma. Transformed lymphomas typically evolve from a nodular pattern to a diffuse pattern.

Tandem transplants usually are defined as the planned administration of two successive cycles of high-dose myeloablative chemotherapy, each followed by infusion of autologous hematopoietic stem cells, whether or not there is evidence of persistent disease following the first treatment cycle. Sometimes, the second cycle may use non-myeloablative immunosuppressive conditioning followed by infusion of allogeneic stem cells.

**High risk (aggressive) T-cell and NK-cell neoplasms**

The T-cell and NK-cell neoplasms are a clinically heterogeneous group of rare disorders, most of which have an aggressive clinical course and poor prognosis. The exception would include the following subtypes which typically have a relatively indolent and protracted course:

- T-cell large granulocyte leukemia (T-LGL), chronic lymphoproliferative disorder of NK cells, early stage mycosis fungoides, primary cutaneous ALCL, and ALK+ ALCL. (11)
Medicare Advantage

For Medicare Advantage, HSCT may be medically necessary for the following:

- Allogeneic HSCT for primary refractory non-Hodgkin’s lymphoma
- Autologous HSCT for resistant non-Hodgkin’s lymphomas or those presenting with poor prognostic features following an initial response.

Facilities performing stem cell transplants on Medicare Advantage members must be accredited by the Foundation for the Accreditation of Cellular Therapy and the Joint Accreditation Committee and compliant with the FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration manual.

Benefit Application

For all business individual transplant facilities may have their own additional requirements or protocols that must be met in order for the patient to be eligible for a transplant at their facility.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


15. Technology Evaluation Center (TEC). Salvage high-dose chemotherapy with allogeneic stem-cell support for relapse or incomplete remission following high-dose chemotherapy with autologous stem-cell transplantation for hematologic malignancies. TEC Assessments 2000; Volume 15, Tab 9.


63. CMS National Coverage Determination (NCD) for Stem Cell Transplantation (110.8.1), 11/10/10.

64. NGS Local Coverage Determination (LCD) for Stem Cell Transplantation (L30183), 11/01/11.