MASSACHUSETTS

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Medical Policy

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

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Related Policies

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Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue[SM] and Medicare PPO Blue[SM] Members

For patients with non-Hodgkin's lymphoma (NHL), B-cell subtypes considered aggressive (except mantle cell lymphoma), either allogeneic hematopoietic stem cell transplantation (HCT) using a myeloablative conditioning regimen or autologous HCT for the following indications 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 adjusted International Prognostic Index score that predicts a high- or high-intermediate risk of relapse.

For patients with mantle cell lymphoma:

- Autologous HCT to consolidate a first remission may be **MEDICALLY NECESSARY**, or
- Allogeneic HCT, myeloablative or reduced-intensity conditioning, as salvage therapy may be **MEDICALLY NECESSARY**.

For patients with NHL B-cell subtypes considered indolent, either allogeneic HCT using a myeloablative conditioning regimen or autologous HCT for the following indications may be **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 HCT as a treatment of NHL may be **MEDICALLY NECESSARY** in patients who meet criteria for an allogeneic HSCT but who do not qualify for a myeloablative allogeneic HCT.

For patients with mature T-cell or NK-cell (peripheral T-cell) lymphoma for the specified indications:
- Autologous HCT may be **MEDICALLY NECESSARY** to consolidate a first complete remission in high-risk peripheral T-cell lymphoma, or
- Autologous or allogeneic HCT (myeloablative or reduced-intensity conditioning) may be **MEDICALLY NECESSARY** as salvage therapy.

The following procedures are **INVESTIGATIONAL**.
- Autologous HCT for patients with mantle cell lymphoma as salvage therapy, or
  Allogeneic HCT for patients with mantle cell lymphoma to consolidate a first remission, or
  Autologous or allogeneic HCT for the following conditions:
  - As initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for any NHL, or
  - 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, or
  - To consolidate a first CR for those with indolent NHL B-cell types.
- Tandem transplants to treat patients with any stage, grade, or subtype of NHL, or
- Allogeneic HCT for patients with peripheral T-cell lymphoma to consolidate a first remission.

Guidelines for use of bone marrow
Stem cells when harvested from the patient's bone marrow prior to marrow ablative therapy or from a donor's marrow after verifying the donor and recipient are well matched with respect to human leukocyte antigens (HLA) may be considered **MEDICALLY NECESSARY**. Verification of well-matched HLA donor and recipient is based on the attending or treating physician's clinical judgment.

Umbilical cord stem cell support as an acceptable cell source for transplants that are otherwise covered for either high-dose chemo with stem cell support, or for bone marrow transplant may be considered **MEDICALLY NECESSARY** when ALL the following are met:
1. Recipient is a child or adult, AND
2. There is no other available stem-cell donor with the same or better matching characteristics, AND
3. Donors may be related or unrelated.

Collection and storage of cord blood from neonate when an allogeneic transplant is "imminent" in an identified recipient with a diagnosis that is consistent with the possible need for allogeneic transplant may be considered **MEDICALLY NECESSARY**.

Exclusions:
1. Facility providing umbilical cord blood that is not in compliance with any existing FDA regulations governing umbilical cord transplants. FDA regulations are currently under development.
2. There is a suitable stem cell donor of equal or superior HLA match, and
3. Storage for future use, in case of a future need for transplant (prophylactic collection and storage).

Prior Authorization Information

Inpatient
- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is **required**.
Commercial PPO and Indemnity	Prior authorization is **required**.
Medicare HMO Blue℠	Prior authorization is **required**.
Medicare PPO Blue℠	Prior authorization is **required**.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

CPT codes:	Code Description
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation

HCPCS Codes

HCPCS codes:	Code Description
S2140	Cord blood harvesting for transplantation; allogeneic
S2142	Cord blood derived stem-cell transplantation, allogeneic
S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

ICD-10 Procedure Codes

ICD-10-PCS procedure codes:	Code Description
30233G0	Transfusion of Autologous Bone Marrow into Peripheral Vein, Percutaneous Approach
30233G1	Transfusion of Nonautologous Bone Marrow into Peripheral Vein, Percutaneous Approach

30233X0	Transfusion of Autologous Cord Blood Stem Cells into Peripheral Vein, Percutaneous Approach
30233X1	Transfusion of Nonautologous Cord Blood Stem Cells into Peripheral Vein, Percutaneous Approach
30233Y0	Transfusion of Autologous Hematopoietic Stem Cells into Peripheral Vein, Percutaneous Approach
30233Y1	Transfusion of Nonautologous Hematopoietic Stem Cells into Peripheral Vein, Percutaneous Approach
30243G0	Transfusion of Autologous Bone Marrow into Central Vein, Percutaneous Approach
30243G1	Transfusion of Nonautologous Bone Marrow into Central Vein, Percutaneous Approach
30243X0	Transfusion of Autologous Cord Blood Stem Cells into Central Vein, Percutaneous Approach
30243X1	Transfusion of Nonautologous Cord Blood Stem Cells into Central Vein, Percutaneous Approach
30243Y0	Transfusion of Autologous Hematopoietic Stem Cells into Central Vein, Percutaneous Approach
30243Y1	Transfusion of Nonautologous Hematopoietic Stem Cells into Central Vein, Percutaneous Approach
30263G0	Transfusion of Autologous Bone Marrow into Central Artery, Percutaneous Approach
30263G1	Transfusion of Nonautologous Bone Marrow into Central Artery, Percutaneous Approach
30263X0	Transfusion of Autologous Cord Blood Stem Cells into Central Artery, Percutaneous Approach
30263X1	Transfusion of Nonautologous Cord Blood Stem Cells into Central Artery, Percutaneous Approach
30263Y0	Transfusion of Autologous Hematopoietic Stem Cells into Central Artery, Percutaneous Approach
30263Y1	Transfusion of Nonautologous Hematopoietic Stem Cells into Central Artery, Percutaneous Approach
3E03305	Introduction of Other Antineoplastic into Peripheral Vein, Percutaneous Approach
3E04305	Introduction of Other Antineoplastic into Central Vein, Percutaneous Approach
3E05305	Introduction of Other Antineoplastic into Peripheral Artery, Percutaneous Approach
3E06305	Introduction of Other Antineoplastic into Central Artery, Percutaneous Approach

Description

Non-Hodgkin Lymphoma

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 was developed to unify different classification systems into one.[1]The Working Formulation divided NHL into low-, intermediate-, and high-grade, with subgroups based on histologic cell type. Because 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 Working Formulation 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 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 cell neoplasms, and Hodgkin lymphoma.

The most recent lymphoma classification is the 2016 WHO classification (see Table 1).[4]

Table 1. Updated WHO Classification (2016)

Classification of Neoplasms
Mature B-cell neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis[a]
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic lymphoma/leukemia, unclassifiable
• *Splenic diffuse red pulp small B-cell lymphoma*
• *Hairy cell leukemia-variant*
Lymphoplasmacytic lymphoma
• Waldenström macroglobulinemia
Monoclonal gammogapthy of undetermined significance, IgM[a]
Heavy chain diseases
• Alpha heavy chain disease
• Gamma heavy chain disease
• Mu heavy chain disease
Monoclonal gammogapthy of undetermined significance, IgG/IgA[a]
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Monoclonal immunglobulin deposition diseases[a]
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma (MZL)
• *Pediatric nodal MZL*
Follicular lymphoma
• *In situ follicular neoplasia*[a]
• *Duodenal-type follicular lymphoma*[a]
Pediatric type follicular lymphoma[a]
• *Large B-cell lymphoma with IRF4 rearrangement*[a]
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
• *In situ mantel cell neoplasia*[a]
Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS)
• *Germinal center B-cell type*[a]
• *Activated B-cell type*[a]
T-cell/histiocyte-rich large B-cell lymphoma
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
Primary cutaneous DLBCL, leg type
ALK [anaplastic lymphoma kinase]-positive large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
HHV8 DLBCL NOS[a]
Burkitt lymphoma
Burkitt-like lymphoma with 11q aberration[a]
High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements[a]
High-grade B-cell lymphoma, NOS[a]
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

Classification of Neoplasms
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
Systemic Epstein-Barr virus-positive T-cell lymphoproliferative of childhood[a]
Hydroa vacciniforme-like lymphoproliferative disorder[a]
Adult T-cell leukemia/ lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma[a]
Indolent T-cell lymphoproliferative disorder of the GI tract[a]
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30-positive T-cell lymphoproliferative disorder
• Lymphomatoid papulosis
• Primary cutaneous anaplastic large-cell lymphoma
Primary cutaneous gamma-delta T-cell lymphoma
Primary cutaneous aggressive epidermotropic CD8-positive cytotoxic T-cell lymphoma[a]
Primary cutaneous acral CD8+ T-cell lymphoma[a]
Primary cutaneous small/medium CD4-positive T-cell lymphoproliferative disorder[a]
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
Follicular T-cell lymphoma[a]
Nodal peripheral T-cell lymphoma with TFH phenotype[a]
Anaplastic large-cell lymphoma (ALCL), ALK-positive
Anaplastic large-cell lymphoma (ALCL), ALK-negative[a]
Breast implant-associated anaplastic large-cell lymphoma[a]

ALK: anaplastic lymphoma kinase; GI: gastrointestinal; Ig: immunoglobulin; NK: natural killer.

[a]Changes from 2008 WHO classification. Provisional entities are listed in italics.

In the United States, B-cell lymphomas represent 80% to 85% of cases of NHL, and T-cell lymphomas represent 15% to 20%. Natural killer lymphomas are relatively rare.[5]

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

Types of NHL

In general, NHL can be divided into two prognostic groups, indolent and aggressive. Indolent NHL has a relatively good prognosis, with a median survival of ten years; however, it is not curable in advanced clinical stages.[1] Early-stage indolent NHL (stage I or II) may be effectively treated with radiotherapy alone.[1] Although indolent NHL is responsive to radiotherapy and chemotherapy, a continuous rate of relapse is seen in advanced stages.[1] These patients can often be treated again 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 1 year or less.

Follicular lymphoma is the most common indolent NHL (70%-80% of cases), and often the terms indolent lymphoma and follicular lymphoma are used synonymously. Also included in the indolent NHL are small lymphocytic lymphoma/chronic lymphocytic lymphoma, lymphoplasmacytic lymphoma, marginal zone lymphomas, and cutaneous T-cell lymphoma.

Aggressive NHL has a shorter natural history; however, 30% to 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.

Risk Assessment
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] Before its development in 1993, the prognosis was predominantly based on disease stage.

Based on the following 5 risk factors prognostic of overall survival (OS) and adjusted for patient age, the IPI defines 4 risk groups: low, low-intermediate, high-intermediate, and high-risk:
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 1 extranodal site.

Risk groups are stratified by a 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 2 or more risk factors have a less than 50% chance of relapse-free survival and OS at 5 years. Age-adjusted IPI 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 2 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 follicular lymphoma, which has multiple independent risk factors for relapse after first complete remission. The proposed and validated Follicular Lymphoma International Prognostic Index contains 5 adverse prognostic factors:

1. Age older than 60 years
2. Ann Arbor stage III or IV disease
3. Hemoglobin level less than 12.0 g/dL
4. More than 4 lymph node areas involved
5. Elevated serum 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 comprises 65% to 68% of NHL and has been recognized for some time now 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 by Banks et al (1992).[9] The number of therapeutic trials is not as numerous for MCL as for other NHL, because it was not widely recognized until the REAL classification. MCL shows a strong predilection for senior men, and most cases (70%) present with disseminated (stage IV) disease; extranodal involvement is common. Localized MCL is quite rare. MCL has a median survival of approximately 2 to 4 years, and although most patients achieve remission

with first-line therapy, relapse inevitably occurs-often within 12 to 18 months. MCL is rarely, if ever, cured with conventional therapy, and no standardized therapeutic approach to MCL is used.

Risk Assessment
Not until recently has a prognostic index been established for patients with MCL. Application of the IPI or Follicular Lymphoma International Prognostic Index system to patients with MCL has shown limitations, which included no separation of some important risk groups. In addition, some of the individual IPI and Follicular Lymphoma International Prognostic Index risk factors, including the 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.

The MCL IPI is based on the following risk factors prognostic for OS.
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 (WBC) count
    - Zero points each are assigned for age younger than 50 years, ECOG Performance Status 0-1, LDH ratio less than 0.67, WBC less than 6700/µL
    - One point each for age 50 to 59 years, LDH ratio 0.67-0.99 U/L, WBC 6700-9999/UL
    - Two points each for age 60 to 69 years, ECOG Performance Status 2-4, LDH ratio 1.00-1.49 U/L, WBC 10,000-14,999/µL
    - Three points each for age 70 years or older, LDH ratio 1.5 U/L or greater, WBC 15,000/UL or more.

MIPI allows separation of three groups with significantly different prognoses[10]:
- 0-3 points denotes low risk, which affects 44% of patients, who have a 5-year overall survival rate of 60% (median overall survival, not reached)
- 4-5 points denotes intermediate risk, which affects 35% of patients, who have a median overall survival of 51 months
- 6-11 points denotes high risk, which affects 21% of patients who have a median overall survival of 29 months

Peripheral T-Cell Lymphoma
Most PTCLs are aggressive and fall into the category of PTCL, unspecified PTCL, or PTCL not otherwise survival, angioimmunoblastic or anaplastic large-cell, which combined make up 60% to 70% of all 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 5 years with standard chemotherapy regimens range from 20% to 35%. The poor results with conventional chemotherapy have prompted exploration of the role of hematopoietic cell transplantation (HCT) as therapy.

Staging
The Ann Arbor staging classification is commonly used to stage lymphomas. Originally developed for Hodgkin disease, the classification was later expanded to include NHL (see Table 2).

Table 2. Ann Arbor Classification

Stage	Involvement
I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE)
II	Involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or localized involvement of extralymphatic organ or site and one or more lymph node regions on the same side of the diaphragm (IIE)
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)
IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement

Treatment for NHL

Hematopoietic Cell Transplantation

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

Conventional Preparative Conditioning for HCT

The conventional practice of allogeneic HCT involves administration of cytotoxic agents (eg, cyclophosphamide, busulfan) with or without total body irradiation; this is performed at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect of this procedure is due to a combination of initial eradication of malignant cells and the subsequent graft-versus-malignancy (GVM) effect that is mediated by non-self-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 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 medically fit to tolerate substantial adverse events 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 HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease, which also increase susceptibility to opportunistic infections. The immune reactivity between donor T-cells and malignant cells is responsible for the GVM effect; it also leads to acute and chronic graft-versus-host disease.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy (with or without radiotherapy) 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 before undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed when the patient's disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

Reduced-Intensity Conditioning for Allogeneic HCT

RIC refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiotherapy that are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is two-fold: to reduce disease burden, and to minimize treatment-related morbidity and nonrelapse mortality 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 nonrelapse mortality and relapse due to residual disease. RIC regimens can be viewed as a continuum-from nearly total myeloablative to minimally myeloablative with lymphoablation-because it tailors its intensity to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT 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 evidence review, RIC refers to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (traditional) regimens.

Summary

Hematopoietic cell transplantation (HCT) refers to a procedure by 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 radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT). They can be harvested from bone

marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although umbilical cord blood is an allogeneic source, the stem cells in it are antigenically “naive” and thus are associated with a lower incidence of rejection or graft-versus-host disease. Umbilical cord blood is discussed in greater detail in policy #285.

For individuals who have indolent B-cell non-Hodgkin lymphomas (NHL) who receive autologous HCT as first-line therapy, the evidence includes randomized trials and systematic reviews. The relevant outcomes are overall survival (OS), disease-specific survival (DSS), change in disease status, morbid events, and treatment-related mortality and morbidity. Randomized trials have not shown a survival advantage with HCT as first-line therapy for indolent B-cell lymphomas; however, randomized studies have shown a survival benefit for relapsed disease. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have aggressive B-cell NHL, excluding mantle cell lymphoma (MCL), who receive autologous HCT as consolidation therapy after first complete remission, the evidence includes randomized trials and systematic reviews. The relevant outcomes are OS, DSS, change in disease status, morbid events, and treatment-related mortality and morbidity. While the data from the randomized trials offer conflicting results, some data have revealed an OS benefit in patients with aggressive B-cell lymphomas (at high- or high-intermediate risk of relapse) who receive HCT to consolidate a first complete remission. Randomized studies of HCT for relapsed aggressive B-cell lymphomas have also shown an OS benefit with the previously described approach. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have NHL, excluding MCL, who receive tandem autologous and allogeneic HCT, the evidence includes several nonrandomized trials. The relevant outcomes are OS, DSS, change in disease status, morbid events, and treatment-related mortality and morbidity. No randomized studies have been conducted on the use of tandem HCT for the treatment of NHL, and the published evidence comprises a limited number of patients. Presently, conclusions on the use of tandem transplants cannot be made about autologous and allogeneic HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have MCL who receive autologous, allogeneic, or tandem HCT, the evidence includes case series. The relevant outcomes are OS, DSS, change in disease status, morbid events, and treatment-related mortality and morbidity. Due in part to the rarity of this disease, randomized trials on the use of HCT for MCL have not been conducted. Case series have shown long-term disease control of this aggressive lymphoma with autologous HCT (with rituximab) to consolidate a first remission; however, the use of autologous HCT in the relapsed setting has not shown improved outcomes. Allogeneic HCT has shown prolonged disease control in the relapsed or refractory setting. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have peripheral T-cell lymphoma (PTCL) who receive autologous or allogeneic HCT, the evidence includes prospective trials and case reports. The relevant outcomes are OS, DSS, change in disease status, morbid events, and treatment-related mortality and morbidity. The role of HCT in PTCL is not well-defined. Few studies have been conducted, and most were performed retrospectively, with a limited number of patients; moreover, the patient populations were heterogeneous and included good- and poor-risk patients in the same study. Patient population and characteristics of the studies can be explained partially by the rarity and heterogeneity of the particular group of lymphomas addressed. Additionally, studies of this nature often mix three types of patients: one type of patient has PTCL not otherwise specified, which has a poorer prognosis; another type has anaplastic lymphoma kinase-positive anaplastic large-cell lymphomas, which has a better prognosis-even with conventional chemotherapy regimens; and a third type has anaplastic lymphoma kinase-negative anaplastic large-cell lymphomas, which has a worse prognosis than anaplastic lymphoma kinase-positive anaplastic large-cell lymphomas (but better than patients with PTCL not otherwise specified).There have been no randomized studies comparing chemotherapy regimens solely in patients with PTCL (ie, some randomized studies have included PTCL with aggressive B-cell lymphomas). For first-line therapy, results from recent phase 2 studies with autologous HCT as consolidation offers the best survival outcomes for patients with high-

risk features; randomized trials to confirm this have not been performed. No relevant data for the use of allogeneic HCT in the first-line setting are available. Patients with relapsed or refractory PTCL are generally considered incurable with chemotherapy alone. In the salvage setting, data have shown that the use of HCT may improve survival outcomes similar to the results seen in corresponding aggressive B-cell lymphomas in the same treatment setting. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Policy History

Date	Action
3/2019	BCBSA National medical policy review. Description, summary and references updated. Policy statements unchanged.
1/2019	Outpatient prior authorization is required for all commercial products including Medicare Advantage. Effective 1/1/2019.
8/2018	Clinical trials for cancer information removed. For information on clinical trials for cancer, see subscriber certificate. 8/13/2018
2/2018	New references added from BCBSA National medical policy.
2/2018	Clarified coding information.
11/2017	BCBSA National medical policy review. "Stem" removed from title and policy. HSCT changed to HCT in Policy statements otherwise unchanged. 11/1/2017
3/2016	New references added from BCBSA National medical policy.
3/2015	New references added from BCBSA National medical policy.
1/2015	Clarified coding information.
5/2014	Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.
4/2013	New references from BCBSA National medical policy.
2/2013	BCBSA National medical policy review. No change in medical policy statement. Effective 2/4/2013.
11/2011-4/2012	Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.
11/1/2011	BCBSA National medical policy review. Changes to policy statements.
7/2011	Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements.
7/2009	New policy, effective 7/2009, describing covered and non-covered indications.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
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Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

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