



Louisiana

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 10/17/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider for patients with non-Hodgkin lymphoma (NHL) B-cell subtypes aggressive (except mantle cell lymphoma), either allogeneic hematopoietic cell transplantation (HCT) using a myeloablative conditioning regimen or autologous hematopoietic cell transplantation (HCT) to be **eligible for coverage**.

Patient Selection Criteria

Coverage eligibility for the use of hematopoietic cell transplantation (HCT) for non-Hodgkin lymphomas (NHLs) will be considered when ANY of the following criteria are met:

- 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; OR
- To achieve or consolidate a complete remission (CR) for those in a chemosensitive first or subsequent relapse; OR
- To consolidate a first complete remission (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:

Based on review of available data, the Company may consider autologous hematopoietic cell transplantation (HCT) to consolidate a first remission to be **eligible for coverage**.

Based on review of available data, the Company may consider allogeneic hematopoietic cell transplantation (HCT), myeloablative or reduced-intensity conditioning (RIC) as salvage therapy to be **eligible for coverage**.

For Patients with Non-Hodgkin Lymphoma (NHL) B-Cell Subtypes:

Based on review of available data, the Company may consider patients with non-Hodgkin lymphoma (NHL) B-cell subtypes indolent, either allogeneic hematopoietic cell transplantation (HCT) using a myeloablative conditioning regimen or autologous hematopoietic cell transplantation (HCT) to be **eligible for coverage**:

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- As salvage therapy for patients who do not achieve complete remission (CR) after first-line treatment (induction) with a full course of standard-dose chemotherapy; OR
- To achieve or consolidate complete remission (CR) for those in a first or subsequent chemosensitive relapse, whether or not their lymphoma has undergone transformation to a higher grade.

Based on review of available data, the Company may consider reduced-intensity conditioning (RIC) allogeneic hematopoietic cell transplantation (HCT) as a treatment of non-Hodgkin lymphoma (NHL) in patients who meet criteria for an allogeneic hematopoietic cell transplantation (HCT) but who do not qualify for a myeloablative allogeneic hematopoietic cell transplantation (HCT) to be **eligible for coverage**. (see Policy Guidelines).

For Patients with Mature T-Cell or Natural Killer (NK)-Cell (Peripheral T-Cell) Neoplasms:

Based on review of available data, the Company may consider autologous hematopoietic cell transplantation (HCT) to consolidate a first complete remission (CR) in high-risk subtypes to be **eligible for coverage**. (see Policy Guidelines).

Based on review of available data, the Company may consider autologous or allogeneic hematopoietic cell transplantation (HCT) (myeloablative or reduced-intensity conditioning [RIC]) as salvage therapy to be **eligible for coverage**.

When Services Are Considered Investigational

Note: Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers either autologous hematopoietic cell transplantation (HCT) or allogeneic hematopoietic cell transplantation (HCT) to be **investigational***:

- As initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for any non-Hodgkin lymphoma (NHL); OR
- To consolidate a first complete remission (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 complete remission (CR) for those with indolent non-Hodgkin lymphoma (NHL) B-cell subtypes.

Based on review of available data, the Company considers tandem transplants to treat patients with any stage, grade, or subtype of non-Hodgkin lymphoma (NHL) to be **investigational.***

For Patients with Mature T-Cell or Natural Killer (NK)-Cell (Peripheral T-Cell) Neoplasms:

Based on review of available data, the Company considers allogeneic hematopoietic cell transplantation (HCT) to consolidate a first remission to be **investigational.***

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For Patients with Mantle Cell Lymphoma (MCL):

Based on review of available data, the Company considers autologous hematopoietic cell transplantation (HCT) as salvage therapy to be **investigational**.*

Based on review of available data, the Company considers allogeneic hematopoietic cell transplantation (HCT) to consolidate a first remission to be **investigational**.*

Blue Cross Blue Shield Association Policy Guidelines:

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

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

A chemosensitive relapse is defined as relapsed 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 2 successive cycles of high-dose myeloablative chemotherapy, each followed by infusion of autologous hematopoietic 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 cells.

The term *salvage therapy* describes therapy given to patients with refractory or relapsed disease. For patients with peripheral T-cell lymphoma, salvage therapy includes patients who do not achieve a complete response (eg, achieve only a partial response, have no response, or have progressive disease) with first-line induction chemotherapy (refractory disease) or who relapse after achieving a complete response with first-line induction chemotherapy. For mantle cell lymphoma, salvage therapy includes patients with progressive disease with first-line induction chemotherapy (refractory disease) or in patients who relapse after a complete or partial response after initial induction chemotherapy, or patients who fail a previous autologous HCT.

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High-Risk (Aggressive) T-Cell and Natural Killer-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.

Background/Overview

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. 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 and an updated version of the REAL system, the new World Health Organization classification. The World Health Organization/REAL classification recognized 3 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 World Health Organization classification (see Table 1).

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
<i>Splenic lymphoma/leukemia, unclassifiable</i>
• <i>Splenic diffuse red pulp small B-cell lymphoma</i>
• <i>Hairy cell leukemia-variant</i>
Lymphoplasmacytic lymphoma
• Waldenström macroglobulinemia
Monoclonal gammopathy of undetermined significance, IgM ^a
Heavy chain diseases
• Alpha heavy chain disease

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Classification of Neoplasms

• Gamma heavy chain disease
• Mu heavy chain disease
Monoclonal gammopathy of undetermined significance, IgG/IgA ^a
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Monoclonal immunoglobulin deposition diseases ^a
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma (MZL)
• <i>Pediatric nodal MZL</i>
Follicular lymphoma
• <i>In situ follicular neoplasia^a</i>
• <i>Duodenal-type follicular lymphoma^a</i>
Pediatric type follicular lymphoma ^a
• <i>Large B-cell lymphoma with IRF4 rearrangement^a</i>
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
• <i>In situ mantle cell neoplasia^a</i>
Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS)
• <i>Germinal center B-cell type^a</i>
• <i>Activated B-cell type^a</i>
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
<i>Primary cutaneous DLBCL, leg type</i>
ALK [anaplastic lymphoma kinase]-positive large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
<i>HHV8 DLBCL NOS^a</i>
Burkitt lymphoma
<i>Burkitt-like lymphoma with 11q aberration^a</i>
High-grade B-cell lymphoma, with <i>MYC</i> and <i>BCL2</i> and/or <i>BCL6</i> rearrangements ^a
High-grade B-cell lymphoma, NOS ^a
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma
Mature T-cell and NK-cell neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
<i>Chronic lymphoproliferative disorder of NK cells</i>
Aggressive NK-cell leukemia
Systemic Epstein-Barr virus-positive T-cell lymphoproliferative of childhood ^a
Hydroa vacciniforme-like lymphoproliferative disorder ^a

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Adult T-cell leukemia/ lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma ^a
<i>Indolent T-cell lymphoproliferative disorder of the GI tract^a</i>
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
<i>Primary cutaneous aggressive epidermotropic CD8-positive cytotoxic T-cell lymphoma^a</i>
<i>Primary cutaneous acral CD8+ T-cell lymphoma^a</i>
<i>Primary cutaneous small/medium CD4-positive T-cell lymphoproliferative disorder^a</i>
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
<i>Follicular T-cell lymphoma^a</i>
<i>Nodal peripheral T-cell lymphoma with TFH phenotype^a</i>
Anaplastic large-cell lymphoma (ALCL), ALK-positive
Anaplastic large-cell lymphoma (ALCL), ALK-negative ^a
<i>Breast implant-associated anaplastic large-cell lymphoma^a</i>

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.

The International Lymphoma Classification Project identified the most common NHL subtypes as follows: diffuse large B-cell lymphoma (DLBCL) 31%, follicular lymphoma 22%, small lymphocytic lymphoma and chronic lymphocytic leukemia 6%, 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.

Types of NHL

In general, NHL can be divided into 2 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. Early-stage indolent NHL (stage I or II) may be effectively treated with radiotherapy alone. Although indolent NHL is responsive to radiotherapy and chemotherapy, a continuous rate of relapse is seen in advanced stages. 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

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used for aggressive, recurrent NHL. Histologic transformation to higher grade lymphoma occurs in up to 70% of patients with low-grade lymphoma, 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. 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). Before its development in 1993, the prognosis was predominantly based on disease stage.

Based on the following 5 risk factors prognostic of overall survival 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 overall survival 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:

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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 5 factors are used to stratify patients into 3 categories of risk: low (0-1 risk factor), intermediate (2 risk factors), or poor (3 or more risk factors).

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 in 1992 by Banks et al. 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 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. Therefore, a new prognostic index for patients with MCL was developed and should prove useful in comparing clinical trial results for MCL.

The MCL International Prognostic Index is based on the following risk factors prognostic for overall survival.

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 to age younger than 50 years, ECOG Performance Status score of 0-1, LDH ratio of less than 0.67 U/L, WBC of less than 6700/ μ L
 - One point each for age 50 to 59 years, LDH ratio of 0.67-0.99 U/L, WBC of 6700-9999/ μ L
 - Two points each for age 60 to 69 years, ECOG Performance Status score of 2-4, LDH ratio of 1.00-1.49 U/L, WBC of 10,000-14,999/ μ L

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- Three points each for age 70 years or older, LDH ratio of 1.5 U/L or greater, WBC of 15,000/ μ L or more.

MCL International Prognostic Index allows separation of 3 groups with significantly different prognoses:

- 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 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 allogenic 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

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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 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 graft-versus-malignancy 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 graft-versus-malignancy 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 graft-versus-malignancy 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 minimal 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,

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reduced-intensity conditioning refers to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (traditional) regimens.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

The U.S. FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

Centers for Medicare and Medicaid Services (CMS)

Medicare has the following national coverage determination for the use of autologous cell transplantation for Hodgkin and non-Hodgkin lymphomas.

- "a) Effective 1989, AuSCT [autologous stem cell transplantation] is considered reasonable and necessary ... for the following conditions and is covered under Medicare for patients with:
1. Acute leukemia in remission who have a high probability of relapse and who have no human leucocyte antigens (HLA)-matched;
 2. Resistant non-Hodgkin's lymphomas or those presenting with poor prognostic features following an initial response;
 3. Recurrent or refractory neuroblastoma; or,
 4. Advanced Hodgkin's disease who have failed conventional therapy and have no HLA-matched donor.
- b) Effective ... 2000, single AuSCT is only covered for Durie-Salmon Stage II or III patients that fit the following requirements:
- Newly diagnosed or responsive multiple myeloma. This includes those patients with previously untreated disease, those with at least a partial response to prior chemotherapy (defined as a 50% decrease either in measurable paraprotein [serum and/or urine] or in bone marrow infiltration, sustained for at least 1 month), and those in responsive relapse; and
 - Adequate cardiac, renal, pulmonary, and hepatic function.
- c) Effective ... 2005, when recognized clinical risk factors are employed to select patients for transplantation, high dose melphalan (HDM) together with AuSCT is reasonable and necessary for Medicare beneficiaries of any age group with primary amyloid light chain (AL) amyloidosis who meet the following criteria:
- Amyloid deposition in 2 or fewer organs; and,
 - Cardiac left ventricular ejection fraction (EF) greater than 45%."

Rationale/Source

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to

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patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

This review has been informed by several TEC Assessments. Since publication of the 2000 Assessment, the classification of non-Hodgkin lymphoma (NHL) has undergone significant changes, and several new and unique subtypes have emerged (eg, MCL, PTCL). The following is a summary of key literature to date.

INDOLENT LYMPHOMAS

Hematopoietic Cell Transplantation as First-Line Treatment for Indolent NHL

Systematic Reviews

In 2012, Al Khabori et al performed a systematic review and meta-analysis of the use of autologous HCT in untreated, advanced follicular lymphoma (FL). Four RCTs comparing autologous HCT with conventional chemotherapy (total N=941 patients) were included. Three trials reported overall survival (OS); moderate quality evidence from these trials did not show improvement in OS with the use of HCT as part of the initial treatment of FL. Adverse events, including treatment-related mortality and the development of myelodysplastic syndrome, acute myeloid leukemia, and solid tumors, did not differ between treatment arms.

In 2012, Schaaf et al performed a systematic review of RCTs comparing autologous HCT with chemotherapy or immunochemotherapy in patients with previously untreated or relapsed FL concerning OS, progression-free survival (PFS), treatment-related mortality, adverse events, and secondary malignancies. Five RCTs involving 1093 patients were included, with 4 trials in previously untreated patients and one in relapsed patients. The quality of the 5 trials was judged to be moderate. There was a statistically significant increase in PFS in previously untreated FL patients in the HCT arm (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.33 to 0.54; $p < 0.001$). However, there was no statistically significant OS advantage (HR=0.97; 95% CI, 0.76 to 1.24; $p = 0.81$). In the 4 trials in previously untreated patients, there were no statistically significant differences between HCT and the control arm in terms of treatment-related

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mortality (relative risk [RR], 1.28; 95% CI, 0.25 to 6.61; $p=0.77$), secondary acute myeloid leukemia/myelodysplastic syndromes (RR=2.87; 95% CI, 0.7 to 11.75; $p=0.14$), or solid cancers (RR=1.20; 95% CI, 0.25 to 5.77; $p=0.82$). Adverse events were rarely reported but were more frequent in patients who underwent HCT. For patients with relapsed FL, there was some evidence from 1 trial with 70 patients that HCT was advantageous regarding PFS (HR=0.30; 95% CI, 0.15 to 0.61) and OS (HR=0.40; 95% CI, 0.18 to 0.89). No results were reported from this trial for treatment-related mortality, adverse events, or secondary cancers.

Randomized Controlled Trials

In 2008, Ladetto et al reported on the results of a phase 3, randomized, multicenter trial of patients with high-risk FL, treated at diagnosis. A total of 134 patients were randomized to rituximab-supplemented high-dose chemotherapy plus autologous HCT or up to 6 courses of cyclophosphamide, doxorubicin (Adriamycin), vincristine (Oncovin), and prednisolone (CHOP) followed by rituximab (CHOP-R). Of these patients, 79% completed HCT and 71% completed CHOP-R. CR was 85% with HCT and 62% with CHOP-R. At a median follow-up of 51 months, the 4-year event-free survival (EFS) rate was 61% for HCT and 28% for CHOP-R, with no difference in OS. Molecular remission (defined as negative results by polymerase chain reaction on ≥ 2 consecutive bone marrow samples spaced 6 months apart in patients who reached CR) was achieved in 80% of HCT and 44% of CHOP-R patients and was the strongest independent outcome predictor. In 71% of the CHOP-R patients who had relapsed, salvage HCT was performed and achieved an 85% CR rate and a 68% 3-year EFS rate.

In 2006, Sebban et al reported on the results of a randomized, multicenter study. A total of 209 patients received cyclophosphamide, doxorubicin, etoposide, prednisolone, interferon plus cyclophosphamide, doxorubicin, etoposide, prednisolone, and 131 patients received CHOP followed by high-dose chemotherapy with total body irradiation and autologous HCT. Response rates were similar in both groups (79% and 78% after induction therapy, respectively). After a median follow-up of 7.5 years, intention-to-treat analysis showed no difference between the arms for OS ($p=0.53$) or EFS ($p=0.11$).

Deconinck et al (2005) investigated the role of autologous HCT as initial therapy in 172 patients with FL considered at high-risk due to the presence of either B symptoms (ie, 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 an immunochemotherapy regimen or a high-dose therapy followed by purged autologous HCT. While the autologous HCT 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.

In 2004, Lenz et al reported on the results of a trial of 307 patients with advanced stage lymphoma in first remission, including FL, MCL, or lymphoplasmacytoid lymphoma. Patients were randomized to consolidative therapy plus autologous HCT or interferon therapy. The 5-year PFS rate was considerably

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higher in the autologous HCT arm (64.7%) than in the interferon arm (33.3%). However, the median follow-up of patients in this trial was too short to permit any comparison of OS.

HCT for Relapsed, Indolent NHL

In most patients with FL relapse, and with relapsed disease, a cure is unlikely, with a median survival of 4.5 years after recurrence. In the European CUP trial (2004), 89 patients with relapsed, nontransformed FL with partial response (PR) or CR after standard induction chemotherapy were randomized to 1 of 3 arms: 3 additional cycles of conventional chemotherapy (n=24), high-dose chemotherapy and unpurged autologous HCT (n=33), or high-dose chemotherapy with purged autologous HCT (n=32). OS rates at 4 years for the chemotherapy vs unpurged vs purged arms were 46%, 71%, and 77%, respectively. Two-year PFS rates were 26%, 58%, and 55%, respectively. No difference was found between the autologous HCT arms. Although several studies have consistently shown improved disease-free survival with autologous HCT for relapsed FL, this study was the first to show a difference in OS benefit.

A 2017 single-center retrospective study by Bozkaya et al analyzed data from 38 patients who were treated between 2004 and 2014 with high-dose chemotherapy followed by autologous HCT. All cases presented refractory or relapsed Hodgkin lymphoma (n=22) or a number of subtypes of NHL (n=18). Among the regimens given to patients were ifosfamide, carboplatin, and etoposide, and carmustine, etoposide, cytosine arabinoside, and melphalan; additionally, doxorubicin, bleomycin, vinblastine, and dacarbazine were administered to Hodgkin lymphoma patients, and R-CHOP was given to those with NHL. Given the small sample size, multivariate analysis was precluded; however, univariate analysis found no statistically significant differences between groups, except regarding chemosensitive vs chemoresistant cases and between patients undergoing ifosfamide, carboplatin, and etoposide and carmustine, etoposide, cytosine arabinoside and melphalan regimens. After salvage therapy, 22 patients showed a PR; 6 patients showed a CR, and 8 had stable disease. The study found that the 5-year OS rate was significantly higher for chemosensitive patients (50%) than for chemoresistant patients (22%; p=0.02); however, given the small size of the population, other analyses were primarily descriptive or showed no statistical significance.

Section Summary: Indolent Lymphomas

Randomized trials have shown no survival advantage to HCT as first-line therapy for indolent B-cell lymphomas; however, randomized studies have shown a survival benefit for relapsed disease.

AGGRESSIVE LYMPHOMAS

HCT for First-Line Therapy for Aggressive NHL

Randomized Controlled Trials

Several randomized trials reported between 1997 and 2002 have compared outcomes of autologous HCT used to consolidate a first CR in patients with intermediate or aggressive NHL, with outcomes of an alternative strategy that delayed transplants until relapse. As summarized in a 2002 editorial, the preponderance of evidence showed that consolidating first CRs with HCT did not improve OS for the full

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population of enrolled patients. However, a 2000 subgroup analysis at 8-year median follow-up focused on 236 patients at high or high-intermediate risk of relapse (based on age-adjusted IPI scores) who were enrolled in the largest of these trials (LNH87-2 protocol). The subgroup analysis reported superior OS (64% vs 49%, respectively; RR=1.51, p=0.04) and disease-free survival (DFS; 55% vs 39%, respectively; RR=1.56, p=0.02) for patients at elevated risk of relapse who received autologous HCT as consolidation therapy.

A large, multigroup, prospective, randomized phase 3 comparison of these strategies (S9704 trial) was designed to confirm results of the subgroup analysis in a larger population with DLBCL at high and high-intermediate risk of relapse. Nevertheless, many clinicians have viewed the LNH87-2 subgroup analysis as sufficient evidence to support the use of autologous HCT to consolidate a first CR when the risk of relapse is high. In contrast, editorials and reviews concluded that available evidence showed no survival benefit from autologous HCT to consolidate the first CR in patients with intermediate or aggressive NHL at low or low-intermediate risk of relapse (using age-adjusted IPI score).

Between 2005 and 2008, several systematic reviews and randomized trials also showed no survival benefit to HCT as first-line therapy for aggressive lymphomas, as summarized next.

Systematic Reviews

Greb et al (2008) conducted a systematic review and meta-analysis to determine whether high-dose chemotherapy with autologous HCT as first-line treatment in patients with aggressive NHL would improve survival compared with conventional chemotherapy. Fifteen RCTs (total N=3079 patients) were eligible for the meta-analysis. Thirteen studies (n=2018 patients) showed significantly higher CR rates in the autologous HCT group (p=0.004). However, autologous HCT did not affect OS when compared with conventional chemotherapy. According to the IPI, subgroup analysis of prognostic groups showed no survival differences between autologous HCT and conventional chemotherapy in 12 trials, and EFS also did not differ between the 2 groups. Despite higher CR rates, the evidence suggested no benefit with autologous HCT as first-line treatment in aggressive NHL.

Randomized Controlled Trials

Betticher et al (2006) reported on the results of a phase 3 multicenter, randomized trial comparing sequential high-dose chemotherapy plus autologous HCT with standard CHOP as first-line therapy in 129 patients with aggressive NHL. Remission rates were similar in the 2 groups, and, after a median observation time of 48 months, there was no difference in OS (46% in the sequential autologous HCT group vs 53% in the group that received CHOP; p=0.48). Sequential autologous HCT did not confer any survival benefit as initial therapy in patients with aggressive NHL.

Baldissera et al (2006) reported on the results of a prospective RCT comparing high-dose chemotherapy plus autologous HCT with conventional chemotherapy as first-line therapy in 56 patients with high-risk aggressive NHL. The 5-year actuarial OS and PFS rates did not differ statistically between the 2 study

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groups; only DFS differed statistically (97% for the autologous HCT group vs 47% for the conventional group; $p=0.02$.)

Olivieri et al (2005) reported on a randomized study of 223 patients with aggressive NHL using upfront high-dose chemotherapy plus autologous HCT vs conventional chemotherapy plus autologous HCT in cases of failure. In the conventional group, 29 patients achieved a PR or no response and went on to receive high-dose chemotherapy plus autologous HCT. With a median follow-up of 62 months, there was no difference in the 7-year probability of survival (60% and 57.8%, $p=0.5$), DFS (62% and 71%, $p=0.2$), or PFS (44.9% and 40.9%, $p=0.7$, all respectively) between the 2 groups. Patients with aggressive NHL did not benefit from upfront autologous HCT.

Results of a phase 3 multicenter randomized trial (SWOG-9704) of autologous HCT as consolidation for aggressive (high-intermediate or high-risk) diffuse B-cell NHL were published in 2013. In this trial, 253 patients received 5 cycles of induction chemotherapy (CHOP with [$n=156$ (47%)] or without rituximab). Those who had at least a PR to 5 cycles of induction therapy were randomized to 3 additional cycles of CHOP ($n=128$) or 1 additional cycle of CHOP followed by autologous HCT ($n=125$). The primary efficacy end points of the trial were two-year PFS and OS. Two-year PFS rates were 69% and 55% in the HCT and control group, respectively (HR control vs HCT=1.72; 95% CI, 1.18 to 2.51; $p=0.005$). The 2-year OS rates in the HCT and control group were 74% and 71%, respectively (HR=1.26; 95% CI, 0.82 to 1.94; $p=0.30$). Unplanned exploratory analyses showed a differential treatment effect by disease risk level. Among high-risk patients, the 2-year OS rate was 82% in the HCT group and 64% in the control group ($p=0.01$). The main results of this trial comport with earlier study results in not discerning a significant effect of early autologous HCT on OS among a group of patients with high-, intermediate-, and high-risk diffuse B-cell NHL. However, the survival curve appeared to plateau among the high-risk HCT patients out to 10 years after study registration. Although this evidence was from exploratory subset analysis, it further supports the efficacy of this approach in such cases compared with nontransplant strategies.

A 2017 single-center cohort study by Strüßmann et al compared high-dose chemotherapy plus subsequent autologous HCT with an early-intensified regimen (6-cycle CHOP-14) that included rituximab and methotrexate in 63 patients with DLBCL and poor prognosis. All patients had an age-adjusted IPI score of 2 or 3, and demographic information was comparable for both cohorts (eg, median ages were 48 and 53 for cohorts 1 and 2, respectively). Four cycles of R-CHOP-21 were administered to cohort 1, followed by high-dose carmustine, etoposide, cytosine arabinoside, and melphalan, and autologous HCT; cohort 2 was initially given 6-cycle CHOP-14, then rituximab and high-dose methotrexate. At 2-year follow-up, PFS and OS rates were compared between cohorts, and patients in cohort 2 had significantly better outcomes, even when adjusted for multiple variables (including that of age-adjusted IPI score). The 2-year PFS rate was 60.6% for those in cohort 1, compared with 93.37% in cohort 2 (HR=7.2; 95% CI, 1.64 to 31.75; $p=0.009$), a finding was also statistically significant in multivariate analysis (HR=8.12; 95% CI, 1.73 to 36; $p=0.006$). The OS rate at 2 years was 69.7% for cohort 1 and 93.3% (HR=5.86; 95% CI, 1.28 to 26.8) after multivariate analysis. Also, patients in cohort 2 showed significantly higher overall response and CR rates (93.3% and

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90%) than did patients in cohort 1 (66.7% and 63.6%), respectively; furthermore, no treatment-related mortality was reported for cohort 2 during follow-up, despite the initial intensive treatment protocol.

A 2017 phase 2 clinical trial (LNH2007-3B) by Casasnovas et al randomized 211 patients to receive a 4-cycle regimen of doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone plus rituximab or R-CHOP14, to be followed by standard immunochemotherapy or autologous HCT. Of the 200 patients who completed the trial, 109 were assigned to doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone plus rituximab and 97 were assigned to R-CHOP14; all patients had confirmed DLBCL and had 2 or 3 risk factors according to age-adjusted IPI. Neither group achieved the primary end point, which was CR greater than 50%, as defined by 2007 International Harmonization Project criteria, with 47% (95% CI, 38% to 67%) of doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone plus rituximab patients and 39% (95% CI, 28% to 54%) showing CR. Investigators noted the disparity between the low response according to International Harmonization Project criteria and the improvement of outcomes predicted by positron emission tomography (PET) results and assessed by change in maximum standard uptake value (Δ SUVmax), suggesting that the latter might be a superior indicator of disease progression than International Harmonization Project criteria. PET scans were performed on all patients at baseline, after 2 cycles of the induction regimen (PET2), and again after 4 cycles of treatment (PET4); patients who showed negative results for both PET2 and PET4 were assigned to standard immunochemotherapy (n=51), while those who showed positive results for PET2 but negative results for PET4 were recommended for autologous HCT (n=40). No statistically significant differences in outcome were observed between these groups; however, investigators observed significant differences in outcomes when they assessed Δ SUVmax in patients. At measurement of PET2, rates of 4-year PFS and OS were higher for patients with Δ SUVmax greater than 66% than for those showing a smaller change in SUVmax (PFS for the respective groups was 80% vs 56%, $p < 0.001$; OS was 87% vs 69% in patients with a Δ SUVmax $< 66\%$, $p = 0.003$). When Δ SUVmax was assessed following PET4, similar improvements were observed: the 4-year PFS rate was 84% in those showing a Δ SUVmax greater than 70%, compared with 35% in those with a Δ SUVmax of 70% or less ($p < 0.001$); likewise, OS rates were 91% and 57% for the respective groups ($p < 0.001$). Differences between the potential treatments (standard chemotherapy, autologous HCT, or salvage therapy) were not statistically significant.

Qualls et al published a small retrospective study in 2017 of 20 individuals (13 men, 7 women) treated with autologous HCT for systemic NHL with some form of central nervous system (CNS) involvement. Most patients presented with DLBCL histology (n=17 [85%]), and CNS involvement varied: the 2 most common types of CNS involvement were parenchymal involvement (n=12 [60%]) and leptomeningeal disease (n=9 [45%]). As an induction regimen, the majority of patients (n=13 [65%]) were given R-CHOP, or, as a treatment for CNS involvement, high-dose methotrexate (n=16 [80%]). The high-dose chemotherapy regimen for all patients included thiotepa, busulfan, and cyclophosphamide, and 6 patients received rituximab plus thiotepa, busulfan, and cyclophosphamide; all patients received autologous HCT during first CR. PFS rates were high at 1-year (84%; 95% CI, 59% to 95%) and 4-year (77%; 95% CI, 48% to 91%) follow-ups. OS rates were similarly high at 1 year (95%; 95% CI, 68% to 99%) and 4 years (82%; 95% CI,

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54% to 94%). The most commonly experienced treatment-related adverse events were febrile neutropenia, which was observed in 80% (n=16) of patients. Despite the small size of the study, the authors noted the rare occurrence of relevant cases, suggesting that the high survival rates observed in the study supported the use of autologous HCT in the first CR.

HCT for Relapsed, Aggressive NHL

Autologous HCT is the treatment of choice for relapsed or refractory aggressive NHL for patients who achieve a CR or PR with second-line therapy. The pivotal trial that established the superiority of autologous HCT for relapsed DLBCL is the 1995 PARMA trial, a prospective randomized study in which 215 patients with chemosensitive disease in first or second relapse of aggressive lymphoma were given 2 courses of conventional chemotherapy. One hundred nine patients responded and were randomized to 4 courses of chemotherapy plus radiotherapy (n=54) or radiotherapy plus intensive chemotherapy and autologous HCT (n=55). The groups did not differ in baseline characteristics. Median follow-up was 63 months. The response rate was 84% in the HCT group and 44% in the nontransplant group. The EFS rate for the transplant group was 46% and 12% in the nontransplant group (p=0.001), and the OS rate was 53% in the transplant group and 32% in the nontransplant group (p=0.038).

Section Summary: Aggressive Lymphomas

Data from randomized trials have shown conflicting results, but some studies have shown an OS benefit with HCT to consolidate a first CR in patients with aggressive B-cell lymphomas at high or high-intermediate risk of relapse. Randomized studies of HCT for relapsed aggressive B-cell lymphomas have shown an OS benefit with this approach.

TANDEM TRANSPLANTS

No prospective controlled studies comparing tandem HCT with single HCT have been identified in the published literature.

A pilot phase 2 trial (2011) evaluated tandem high-dose therapy with stem cell support between 1994 and 1999 in 45 patients with untreated aggressive NHL and an age-adjusted IPI of 3. After induction, responders underwent tandem autologous transplantation; 31 of 41 evaluable patients completed the program. There were 4 toxicity-related deaths. The primary end point of the trial was CR rate, which was 49%. With a median follow-up of 114 months for surviving patients, the OS rate was 51%, and 19 (86%) of the 22 patients who reached a CR were alive and relapse-free. Prospective evaluation of the quality of life and comorbidities of surviving patients did not reveal long-term toxicities.

A pilot study in 2005 evaluated 41 patients with poor-risk NHL and Hodgkin disease who were given tandem high-dose chemotherapy and autologous HCT. Thirty-one (76%) patients completed both transplants. The overall toxicity-related death rate was 12%. The study evaluated the maximally tolerated dose of the chemotherapeutic regimen and did not compare tandem with single transplants for NHL.

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Tarella et al (2007) reported on a multicenter, nonrandomized, prospective trial consisting of 112 patients with previously untreated DLBCL and age-adjusted IPI score of 2 or 3. All patients received rituximab-supplemented, early-intensified high-dose chemotherapy with multiple autologous HCT. Although the treatment regimen appeared to improve patients' life expectancy, the comparisons were made with historical controls who had received conventional chemotherapy.

A 2013 retrospective analysis of 34 high-risk NHL patients who underwent autologous HCT followed closely by reduced-intensity conditioning allogeneic HCT (allo-HCT) evaluated patients treated from 2002 to 2010. In this study, researchers identified appropriate allogeneic donors at the initiation of the salvage regimen. Patients' median age was 47 years. Histologic subtypes were: diffuse large B-cell (n=5), follicular (n=14), transformed follicular (n=4), mantle cell (n=5), plasmacytoid lymphoma (n=1), anaplastic large T-cell (n=2), and peripheral T-cell (n=3). Human leukocyte antigen-identical sibling donors were located for 29 patients, and 10 of 10 matched unrelated individuals were identified for 5 cases. The median interval between autologous HCT and allo-HCT was 77 days (range, 36-197 days). At a median follow-up of 46 months since allo-HCT, the 5-year OS rate was 77%, and the PFS rate was 68%. Six patients experienced disease relapse or progression, the 100-day treatment-related mortality was 0%, and 2-year treatment-related mortality incidence was 6%. These results suggested tandem autologous-allogeneic transplantation is feasible in high-risk NHL patients having a human leukocyte antigen-identical donor, but further study is necessary to establish its role in this setting.

Section Summary: Tandem Transplants

No randomized studies have been conducted on the use of tandem HCT for the treatment of NHL, and the published evidence comprises small numbers of patients. Therefore, the data on tandem transplants are insufficient to determine outcomes with this type of treatment.

NHL SUBTYPES

Several subtypes have emerged with unique clinical and biologic features that are addressed separately herein (specifically MCL and PTCL).

Mantle Cell Lymphoma

Autologous HCT

To improve outcomes of MCL, several phase 2 trials have investigated the efficacy of autologous HCT, with published results differing substantially. Some studies found no benefit to HCT, and others suggested an EFS advantage, at least in a subset of patients.¹⁰ The differing results were likely due to different time points of transplant (first vs second remission) and patient selection criteria.

In 2005, the results of the first randomized trial were reported by Dreyling et al of the European MCL Network. A total of 122 patients with MCL received autologous HCT or interferon as consolidation therapy in first CR or PR. Among these patients, 43% had a low-risk, 11% had a high-intermediate risk, and 6% had a high-risk profile. Autologous HCT resulted in a PR rate of 17% and a CR rate of 81% (vs PR of 62% and CR

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of 37% with interferon). Survival curves for time to treatment failure after randomization showed that autologous HCT was superior to interferon ($p=0.003$). There was also a significant improvement in the 3-year PFS rate in the autologous HCT arm (54%) vs the interferon arm (25%; $p=0.01$). At the time of the reporting, no advantage was seen in OS, with 3-year OS rates of 83% and 77%, respectively. The results also suggested that the impact of autologous HCT could depend on the patient's remission status before the transplant, with a median PFS of 46 months in patients in CR and 33 months in patients in PR.

Till et al (2008) reported on the outcomes for 56 patients with MCL treated with induction chemotherapy plus cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) with or without rituximab followed by autologous HCT in first CR or PR ($n=21$), CHOP with or without rituximab followed by autologous HCT in first CR or PR ($n=15$), or autologous HCT following disease progression ($n=20$). OS and PFS rates at 3 years among patients transplanted in CR or PR were 93% and 63% compared with 46% and 36%, all respectively, for patients transplanted with relapsed or refractory disease. The hazard of mortality among patients transplanted with relapsed or refractory disease was 6.1 times that of patients transplanted in first CR or PR ($p<0.001$).

Geisler et al (2008) reported on 160 previously untreated patients with MCL with dose-intensified induction immunochemotherapy. Responders received high-dose chemotherapy with in vivo purged autologous HCT. OS and CR rates were achieved in 96% and 54%, respectively. The 6-year OS, EFS, and PFS rates were 70%, 56%, and 66%, respectively, with no relapses occurring after 5 years.

Evens et al (2008) reported on 25 untreated patients with MCL who received induction chemotherapy, with an overall response rate of 74%. Seventeen patients received a consolidative autologous ($n=13$) or allogeneic ($n=4$) HCT. Five-year EFS and OS rates for all patients were 35% and 50%, respectively. After a median follow-up of 66 months, the 5-year EFS and OS rates for patients who received autologous HCT were 54% and 75%, respectively.

In a 2017 retrospective case series of 268 patients drawn from the GELTAMO registry and 35 hospitals in Spain, García-Noblejas et al evaluated the response of individuals with MCL to autologous HCT as first-line treatment. Investigators noted a significant improvement in PFS for patients who underwent transplantation during first CR, compared with patients with other disease statuses (ie, PR, chemosensitive, chemorefractory): in univariate analysis, PFS for first CR patients was 48 months (95% CI, 37 to 62 months) compared with 26 months (95% CI, 66 to 128 months) for other statuses ($p=0.01$). There was a similar association between first CR status and OS, compared with other statuses: 97 months vs 57 months ($p=0.03$). When adjusted for multiple variables, both associations were also statistically significant (RR for PFS=1.6 [95% CI, 1.1 to 2.2], $p=0.015$ vs RR for OS=0.8 [95% CI, 1.2 to 2.7], $p=0.003$). During univariate analysis, prior exposure to rituximab was associated with a greater PFS and OS (respectively, $p=0.02$; $p<0.001$); however, this association was confirmed by multivariate analysis because of the limited data on rituximab in all patients. The investigators noted that improvements in survival rates were restricted to patients who received transplantation during first CR; for more uncertain statuses (eg, PR or

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chemosensitivity), the positive association disappeared. However, in 70% of the patients who received transplants and were chemosensitive or achieved a PR, CR was achieved posttransplantation, supporting the use of autologous HCT in patients with CR or near CR.

Allo-HCT

Several studies have assessed allo-HCT with RIC. Khouri et al (2003) reported on results of allo-HCT with RIC in 18 patients with relapsed MCL; after a median follow-up of 26 months, the actuarial probability of EFS was 82% at 3 years. Maris et al (2004) evaluated allo-HCT in 33 patients with relapsed and recurrent MCL. At 2 years, the relapse and nonrelapse mortality rates were 9% and 24%, respectively, and the OS and DFS rates were 65% and 60%, respectively.

Tandem Autologous HCT and Allo-HCT

Two recent major therapeutic advances have substantially altered the outlook of patients with MCL: (1) the introduction of rituximab, which in combination with chemotherapy, has improved the results of both first-line and salvage treatments for MCL; and (2) the combination of rituximab and hyper-CVAD, which is capable of achieving CR rates of up to 90% in the first-line setting, with a prolonged 5-year failure-free survival rate of 60% in younger patients.

Tam et al (2009) reported on a retrospective study that included all patients with MCL who had undergone HCT in sequential phase 2 protocols (autologous or nonmyeloablative allogeneic) at a university cancer center between 1990 and 2007. The approach to transplantation was risk-adapted and based primarily on the patient's treatment status. Autologous HCT was performed as consolidation therapy for patients in the first remission after chemotherapy (1990-2001). From 2001 onward, because of the favorable clinical outcomes found with rituximab (R)-hyper-CVAD chemotherapy, autologous HCT was performed only in patients not in CR after R-hyper-CVAD and in patients who had received less intensive induction chemotherapy (eg, CHOP-R). For patients with relapsed or primary refractory MCL, autologous HCT was performed before the use of nonmyeloablative allogeneic in 1997. After 1997, nonmyeloablative allogeneic was performed whenever a histocompatible donor was available. Patients generally underwent autologous HCT up to the age of 70 and allo-HCT with RIC up to the age of 65 years. Since 2004, patients up to the age of 75 years could receive an autologous transplant. The study included 121 patients with MCL: 50 who underwent autologous HCT in first CR (46%) or PR (54%) (AUTO1), 36 who underwent autologous HCT for relapsed or refractory disease (AUTO2), and 35 who underwent nonmyeloablative allo-HCT for relapsed or refractory disease. The ages at transplantation were similar in all 3 groups (median, 57 years [range, 38-73 years] for AUTO1; median, 59 years [range, 42-76 years] for AUTO2; median, 58 years [range, 43-68 years] for nonmyeloablative allo-HCT).

For the AUTO1 group, at a median follow-up of 6 years, the actuarial PFS and OS rates were 39% and 61%, respectively, with median PFS and OS durations of 42 months and 93 months. Of the AUTO2 patients, 31% did not respond to initial chemotherapy but did experience a PR or better to salvage therapy with hyper-CVAD (n=6), R-hyper-CVAD (n=4), or methotrexate and ara-C (n=1). Seventeen (47%) patients

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were in their second remission, 3 (8%) were in their third or subsequent remission, and 5 (14%) had a chemorefractory relapse and were transplanted in less than partial remission. The actuarial 6-year PFS and OS rates were 10% and 35%, respectively ($p=0.01$ and 0.02 vs AUTO1), and the median PFS and OS durations were 27 and 52 months, respectively. These inferior results for both PFS and OS compared with AUTO1 patients were confirmed in a multivariate analysis that accounted for differences in baseline factors. Of the patients who underwent nonmyeloablative allo-HCT for relapsed or refractory MCL, 20% did not respond to initial chemotherapy but experienced a PR or better to salvage therapy with R-hyper-CVAD. Thirty-one percent were in the second remission, 31% were in third or subsequent remission, and 17% had a refractory relapse and received a transplant in less than PR. With a median follow-up of 56 months (range, 19-110 months), the median PFS duration was 60 months, and the median OS had not yet been reached. The 6-year actuarial PFS rate was 46%, and the 6-year actuarial OS rate was 53%. Plateaus in the survival curves were observed for both PFS and OS, with no relapses or deaths occurring in 9 patients followed between 63 and 110 months. These outcomes were significantly superior to that of AUTO2 patients, whereby relapses and deaths occurred continuously ($p=0.01$ for PFS; $p=0.005$ for OS [4-year landmark for OS]). Compared with AUTO1 patients, the patients who received allo-HCT with RIC had an initially lower OS; however, this reversed at 8 years among nonmyeloablative allogeneic patients.

This study provided evidence that MCL may be curable in both the first-line and salvage settings. In chemotherapy-naïve patients, the results showed that rituximab plus autologous HCT in the first remission might result in long-term disease control, with only 1 relapse occurring among 11 patients followed between 2 years and 8 years, in contrast to that of autologous transplantation without rituximab, in which relapses occurred continuously. In contrast to first-line transplantation, the outcomes of autologous transplantation in patients with relapsed or refractory MCL remain unsatisfactory, with no evidence of a cured fraction on survival curves. The results of autologous and nonmyeloablative allo-HCT in patients with relapsed or refractory MCL also differed markedly. Patients receiving a nonmyeloablative allogeneic transplant showed significantly superior disease control and a disease-free plateau, extending between 5 years and 9 years; whereas patients who received an autologous transplant had a median remission of 2 years and experienced a continuous pattern of relapse. Therefore, nonmyeloablative allo-HCT might be salvaging treatment option for patients no longer curable with maximum cytotoxic strategies.

As noted in the 2009 Tam study, review articles on high-dose therapy for MCL have affirmed the finding in several studies of a superior result of transplantation in first CR (autologous or allogeneic) rather than in the relapsed setting, and that intensive immunochemotherapy as induction therapy preceding high-dose therapy plus autologous HCT is indicated. Also noted were the results of the use of allo-HCT with RIC in the relapsed setting, showing survival plateaus and suggesting curative potential, and suggesting benefit in the use of this approach in younger, fit patients with relapsed MCL.

Section Summary: Mantle Cell Lymphoma

Due in part to the relative rarity of the disease, randomized studies on the use of HCT in MCL have not been conducted. Case series have shown long-term disease control of this aggressive lymphoma with the

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use of autologous HCT (with rituximab) to consolidate a first remission; however, the use of autologous HCT in the relapsed setting has not shown improved outcomes. Allo-HCT has shown prolonged disease control in the relapsed or refractory setting.

PTCL (Mature T-Cell or Natural Killer Cell Neoplasms)

First-Line Autologous HCT (Newly Diagnosed)

Only a few prospective studies with small numbers of patients have investigated autologous HCT in patients with aggressive PTCL. The results are described next.

Reimer et al (2009) conducted a large prospective study of 83 patients with PTCL from multiple centers to undergo autologous HCT as first-line therapy. Patients had various histologies, including PTCL-NOS (not otherwise specified) (n=32), angioimmunoblastic (n=27), anaplastic lymphoma kinase–anaplastic large-cell lymphomas (ALCL) (n=13), and the remainder with extranodal subtypes. Sixty-six percent of the patients received the transplant (for those who chose not to receive the transplant, they cited their progression of the disease as the main reason for not doing so.) Of the patients who proceeded to transplant, 32 were in CR and 33 in PR. The treatment-related mortality rate was 3.6%. Median follow-up was 33 months and estimated 3-year OS and PFS rates were 48% and 36%, respectively.

Corradini et al (2006) reported on the results of 2 phase 2 studies involving 62 patients with advanced stage PTCL at diagnosis. In an intention-to-treat analysis, 46 (74%) of the 62 completed the whole program. Sixteen patients failed to undergo transplant due to early disease progression and/or toxicity. Pretransplant, 56% of patients were in CR and 16% in PR. Median follow-up was 76 months, with estimated 12-year OS, DFS, and EFS rates of 34%, 55%, and 30%, respectively. Five-year EFS and OS rates were 40% and 50%, respectively. Multivariate analysis revealed that patients who achieved CR before HCT had a statistically significant benefit in OS and EFS ($p < 0.001$).

Mercadal et al (2008) reported on the results of a phase 2 trial involving 41 patients diagnosed consecutively with PTCL (median age, 47 years). Patients who responded to induction chemotherapy (CR or PR) went on to autologous HCT. Twenty-four patients responded (CR n=20, PR n=4). Seventeen of these 24 underwent HCT (the remaining patients did not, for various reasons including lack of stem cell mobilization, toxicity, and early relapse). For patients who completed the entire procedure, CR was 51% and PR, 7%. Median follow-up was 3.2 years (range, 0.6-8.1 years), and 5 of 21 CR patients relapsed, and 2 died in CR due to a secondary malignancy. The 4-year PFS rate was 30% (95% CI, 15% to 45%), and the OS rate was 39% (95% CI, 22% to 56%). No difference in OS was noted among the 24 patients eligible for transplant, 17 of whom did, and 7 of whom did not undergo a transplant.

A prospective phase 2 trial by Rodriguez et al (2007) showed that autologous HCT as first-line consolidation therapy improved treatment outcome in patients responding to induction therapy. Nineteen of 26 patients who showed CR or PR to induction therapy received an autologous HCT. At 2 years posttransplant, OS, PFS, and DFS rates were 84%, 56%, and 63%, respectively.

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Salvage (Relapsed or Refractory) Autologous HCT

Kewalramani et al (2006) retrospectively compared results for 24 consecutive patients who had PTCL and underwent autologous HCT for relapsed or refractory disease after responding to second-line therapy with the results of 86 consecutive patients who had chemosensitive relapsed or primary refractory DLBCL. Patients with less aggressive histologies (eg, ALCL expressing the anaplastic lymphoma kinase protein) were excluded. Median follow-up was 6 years, and the 5-year PFS rates for PTCL and DLBCL were 24% and 34%, respectively ($p=0.14$). OS rates were 33% and 39%, respectively. Disease progression occurred in 83% of patients with PTCL and 65% of patients with DLBCL ($p=0.13$). In a univariate analysis of survival for patients with PTCL, response to second-line therapy and the second-line age-adjusted IPI score were prognostic for both PFS and OS. The outcomes for PTCL and DLBCL patients were similar when stratified by the second-line age-adjusted IPI score, in contrast to patients undergoing first-line chemotherapy, where T-cell histology consistently confers a poorer prognosis across IPI subgroups.

Song et al (2003) compared the outcomes of 36 patients who had PTCL who underwent autologous HCT with 97 patients who had relapsed DLBCL. Of patients with PTCL, 27 were at first relapse, 2 at greater than 1 relapse and 7 had the primary refractory disease. Twenty patients had unspecified PTCL, nine had ALCL, and the remainder a mixture of rarer subtypes. Baseline patient characteristics were similar between the PTCL and DLBCL groups. Three-year OS and EFS rates were 48% and 37%, respectively, for PTCL and 53% and 42% for DLBCL ($p=0.41$ and 0.29 , respectively). The patients with unspecified PTCL had an inferior EFS rate when compared with the DLBCL patients (23%, $p=0.028$), and those with ALCL had a nonsignificant trend for improved EFS (67%, $p=0.41$).

Rodriguez et al (2007) reported on the largest series of patients with refractory or relapsed PTCL who received an autologous HCT. One hundred twenty-three patients were derived from registry data between 1990 and 2004. Response to transplantation was as follows: in patients in whom response could be assessed (119/123), 73% achieved a CR, 11% a PR, and transplant failed to produce benefit 16% of patients with stable or progressive disease. Median follow-up was 61 months (range, 0-182 months). The 5-year PFS rate was 34% (95% CI, 25% to 44%) and the 5-year OS rate was 45% (95% CI, 36% to 55%). The DFS rate at 5 years for complete responders was 47% (95% CI, 35% to 58%).

First-Line Allo-HCT

A 2006 review of the impact of HCT in PTCLs found that no relevant data on the use of allo-HCT in the front-line setting. To further investigate the role of HCT in previously untreated PTCL, the Die Deutsche Studiengruppe für Hochmaligne Non-Hodgkin-Lymphome (German High-grade NHL Study Group) initiated a prospective randomized multicenter trial in 2010 comparing upfront autologous HCT with allo-HCT following induction chemotherapy.

Salvage (Relapsed or Refractory) Allo-HCT

For relapsing and refractory PTCL, data on the use of allo-HCT consist of case reports and a number of retrospective series with at least ten patients.

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Jacobsen et al (2011) reported on a single-center experience over 12 years using allo-HCT in 52 patients with PTCL or advanced mycosis fungoides/Sézary syndrome. Patients had a variety of disease subtypes, including nodal and extranodal histologies. Eleven patients had undergone a prior autologous HCT. At the time of the allo-HCT, 23 (44%) patients were in first, or subsequent CR and 16 (31%) had a PR. Thirty-one (60%) patients underwent myeloablative conditioning, and 21 (40%) underwent RIC. The median follow-up was 49 months. Three-year PFS rate was 30% (45% in patients with nodal histologies, 6% in patients with extranodal histologies). The OS rate at 3 years was 41% for all patients. The evidence suggested allo-HCT can produce long-term remissions in relapsed/refractory T-cell lymphoma; plateaus in both OS and PFS curves suggested that allo-HCT might be curative in a select group of patients.

Kyriakou et al (2009) reported on the outcomes of 45 patients with angioimmunoblastic lymphoma who were in the European Group for Blood and Marrow Transplantation database and had undergone an allo-HCT between 1998 and 2005. Angioimmunoblastic lymphoma is characterized by an aggressive clinical course and carries a poor prognosis; with chemotherapy, the OS rate is less than 30% at 5 years. Eleven patients had failed a prior autologous transplant. Twenty-five patients underwent myeloablative and 20 RIC. Nonrelapse mortality rates were 18%, 22%, and 25% at 3, 6, and 12 months, respectively. The median follow-up time for the surviving patients was 29 months (range, 6-76 months). The estimated OS rates at 1 and 3 years were 66% and 64%, respectively. OS for chemotherapy-sensitive patients was significantly better at 81% at 3 years.

Corradini et al (2004) reported on outcomes for 17 patients with relapsed or refractory PTCL who underwent a reduced-intensity allo-HCT. Median age was 41 years (range, 23-60 years). Two of the patients had the primary chemorefractory disease, 15 had relapsed disease, and 8 had disease relapse after a prior autologous HCT. After a median follow-up of 28 months (range, 3-57 months), 14 patients were alive. PFS and OS rates at 3 years were 64% (95% CI, 39% to 89%) and 81% (95% CI, 62% to 100%), respectively. In this initial series, 15 of the 17 patients had the chemotherapy-sensitive disease before transplant. In an update of their experience in 35 patients with a median follow-up of 44 months, PFS and OS rates were 49% and 54%, respectively.

Le Gouill et al (2008) reported on a large retrospective series of patients with different aggressive histologic subtypes of PTCL who underwent allo-HCT. Seventy-seven patients from 20 French centers who underwent transplant between 1988 and 2006 were included. Median age at diagnosis was 36 years (range, 12-61 years). Median follow-up was 43 months (range, 3.5-195 months). Fifty-seven patients received a myeloablative conditioning regimen. All patients had received at least 1 line of therapy before the allo-HCT, including an autologous HCT in 25% of cases. Five-year toxicity-related mortality incidence was 33% (95% CI, 24% to 46%). Overall 5-year OS and EFS rates were 57% (95% CI, 45% to 68%) and 53% (95% CI, 4% to 64%), respectively. There was a large variation in OS and EFS rates by the histopathologic subtypes: 5-year OS and EFS rates were 80% (95% CI, 39% to 94%) and 80% (95% CI, 39% to 94%) for patients with angioimmunoblastic T-cell lymphoma, 63% (95% CI, 41% to 79%) and 58% (95% CI, 35% to 75%) for PTCL-NOS, and 55% (95% CI, 35% to 72%), and 48% (95% CI, 28% to 65%) for ALCL patients,

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respectively. The 5-year OS rate for other histopathologic subtypes (n=12) was 33% (95% CI, 8% to 58%), and four of these patients were still alive in CR. All patients who could not achieve CR after allo-HCT died within 10 months of disease progression. In a multivariate analysis, the strongest predictors of OS were a chemotherapy-resistant disease at the time of the allogeneic transplant and the occurrence of severe (grade 3 or 4) acute graft-versus-host disease.

Section Summary: PTCL (Mature T-Cell or Natural Killer Cell Neoplasms)

The role of HCT in PTCL is not well-defined. Few studies have been conducted, many of these retrospectively, with small numbers of patients and heterogeneous patient populations including good- and poor-risk patients in the same study. This is partly due to the rarity and heterogeneity of this group of lymphomas. In particular, studies often mix patients with PTCL-NOS, which has a poorer prognosis, with patients with *ALK*-positive ALCL, which has a better prognosis (even with conventional chemotherapy regimens), and *ALK*-negative ALCL patients who have a worse prognosis than *ALK*-positive ALCL but better than PTCL-NOS patients.

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).

Reviews have summarized larger studies (2009, 2011) on the use of HCT as first-line (newly diagnosed) and salvage therapy for PTCL. For first-line therapy, results from phase 2 studies using autologous HCT as consolidation therapy offer the best survival outcomes for patients with high-risk features; confirmatory randomized trials have not been performed. No relevant data on the use of allo-HCT in the first-line setting are available.

Approximately 30% to 60% of these patients do not reach transplantation due to early disease progression or toxicity, and 20% to 30% relapse after transplantation. Patients with relapsed or refractory disease are generally considered incurable with chemotherapy alone. In the salvage setting, the data show 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.

SUMMARY OF EVIDENCE

For individuals who have indolent B-cell NHL who receive autologous HCT as first-line therapy, the evidence includes randomized trials and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, 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 MCL, who receive autologous HCT as consolidation therapy after first complete remission, the evidence includes randomized trials and systematic

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reviews. Relevant outcomes are overall survival, disease-specific survival, 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 overall survival 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 overall survival 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 HCT and allo-HCT, the evidence includes several nonrandomized trials. Relevant outcomes are overall survival, disease-specific survival, 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 allo-HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have mantle cell lymphoma who receive autologous, allogeneic, or tandem HCT, the evidence includes case series. Relevant outcomes are overall survival, disease-specific survival, 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. Allo-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 PTCL who receive autologous HCT or allo-HCT, the evidence includes prospective trials and case reports. Relevant outcomes are overall survival, disease-specific survival, 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 3 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

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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.

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Policy History

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12/06/2001	Medical Policy Committee review
03/25/2002	Managed Care Advisory Council approval
06/24/2002	Format revision. No substance change to policy
05/07/2004	Medical Director Review
05/18/2004	Medical Policy Committee review. Format revision. High-Dose Chemotherapy and Hematopoietic Stem-Cell Support for Non-Hodgkin's Lymphoma policy developed separately from current HDC with Hematopoietic Stem-cell Support policy. No substance change to policy
06/28/2004	Managed Care Advisory Council approval
08/03/2005	Medical Director review
08/16/2005	Medical Policy Committee review. Format revision. Appendix A added Coverage eligibility unchanged
08/24/2005	Managed Care Advisory Council approval
07/07/2006	Format revision including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
08/02/2006	Medical Director review
08/09/2006	Medical Policy Committee approval. Background and rationale/source updated to reflect current literature review.
07/10/2007	Medical Director review
07/18/2007	Medical Policy Committee approval. Coverage eligibility unchanged.
07/02/2008	Medical Director review
07/16/2008	Medical Policy Committee review. Older WHO/REAL and IWF classification schemes replaced by updated WHO/REAL classification and Ann Arbor staging schemes. Minor, nonsubstantive wording changes made to the Policy statements to de-emphasize the older classification systems; "peripheral T-cell lymphoma (PTCL) at any stage of disease" added as investigational indication. Information about non-myeloablative (RIC) regimens added. "High-Dose Chemotherapy" removed from policy title.
07/02/2009	Medical Director review
07/22/2009	Medical Policy Committee review. Policy statement revised to indicate that autologous SCT may be considered medically necessary in some cases of mantle cell lymphoma and that reduced-intensity chemotherapy allogeneic SCT may be medically necessary under specific conditions.
07/01/2010	Medical Policy Committee approval
07/21/2010	Medical Policy Implementation Committee approval. No change to coverage.
08/04/2011	Medical Policy Committee approval
08/17/2011	Medical Policy Implementation Committee approval. Policy statements revised to specifically break out mantle cell lymphoma (investigational statements added for autologous as salvage therapy and

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allogeneic to consolidate a first remission and medically necessary statement added for allogeneic as salvage therapy) and peripheral T-cell lymphoma (added statements as medically necessary for autologous to consolidate first remission in specific situations and autologous and allogeneic as salvage therapy, and as investigational regarding allogeneic HSCT to consolidate a first complete remission).

08/02/2012 Medical Policy Committee review
 08/15/2012 Medical Policy Implementation Committee approval. Coverage eligibility statement clarification that peripheral T-cell lymphomas encompass mature T-cell and NK-cell neoplasms.
 03/04/2013 Coding updated
 08/01/2013 Medical Policy Committee review
 08/21/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
 09/04/2014 Medical Policy Committee review
 09/17/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
 08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
 09/03/2015 Medical Policy Committee review
 09/23/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
 10/06/2016 Medical Policy Committee review
 10/19/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
 01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
 10/05/2017 Medical Policy Committee review
 10/18/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
 10/04/2018 Medical Policy Committee review
 10/17/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
 Next Scheduled Review Date: 10/2019

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38230, 38232, 38240, 38241, 38242, 38243
HCPCS	S2140, S2142, S2150
ICD-10 Diagnosis	C82.00-C82.99 C83.00-C83.99 C84.40-C84.99 C84.A0-C84.A9
	C84.Z0-C84.Z9 C85.10-C85.99 C86.0-C86.66 C88.4

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. Reference to federal regulations.

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- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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