8.01.20	Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas		
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Policy Statement

I. For individuals with non-Hodgkin lymphoma (NHL) B-cell subtypes considered aggressive (except mantle cell lymphoma), either allogeneic hematopoietic cell transplantation (HCT) using a myeloablative conditioning regimen or autologous HCT may be considered **medically necessary** for **any** of the following reasons:
   A. As salvage therapy for individuals who do not achieve a complete remission (CR) after first-line treatment (induction) with a full course of standard-dose chemotherapy
   B. To achieve or consolidate a CR for those in a chemosensitive first or subsequent relapse
   C. To consolidate a first CR in individuals 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 individuals with mantle cell lymphoma:

II. Autologous HCT may be considered **medically necessary** to consolidate a first remission
III. Allogeneic HCT, with myeloablative or reduced-intensity conditioning, may be considered **medically necessary** as salvage therapy
IV. Autologous HCT is considered **investigational** as salvage therapy
V. Allogeneic HCT is considered **investigational** to consolidate a first remission

VI. For individuals with NHL B-cell subtypes considered indolent, either allogeneic HCT using a myeloablative conditioning regimen or autologous HCT may be considered **medically necessary either** of the following reasons:
   A. As salvage therapy for individuals who do not achieve CR after first-line treatment (induction) with a full course of standard-dose chemotherapy
   B. To achieve or consolidate CR for those in a first or subsequent chemosensitive relapse, whether or not their lymphoma has transformed to a higher grade

VII. Either autologous HCT or allogeneic HCT is considered **investigational** for **any** of the following:
   A. As initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for any NHL
   B. To consolidate a first CR for individuals with diffuse large B-cell lymphoma and an International Prognostic Index score that predicts a low- or low-intermediate risk of relapse
   C. To consolidate a first CR for those with indolent NHL B-cell subtypes

For individuals with mature T-cell or natural killer cell (peripheral T-cell) neoplasms:

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

For individuals with hepatosplenic T-cell lymphoma:

XI. Allogenic HCT may be considered **medically necessary** to consolidate a first CR or partial response.
XII. Autologous HCT may be considered **medically necessary** to consolidate a first response if a suitable donor is not available or for individuals who are ineligible for allogeneic HCT.

XIII. Autologous or allogeneic HCT as initial therapy (i.e., without a full course of standard-dose induction chemotherapy) is considered **investigational**.

XI. Reduced-intensity conditioning with allogeneic HCT may be considered **medically necessary** as a treatment of NHL in individuals who meet criteria for an allogeneic HCT but who do not qualify for a myeloablative allogeneic HCT (see Policy Guidelines section).

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

Note: Small lymphocytic lymphoma (SLL) may be considered a node-based variant of chronic lymphocytic leukemia (CLL). Therefore, small lymphocytic lymphoma is considered along with chronic lymphocytic leukemia in Blue Shield of California Medical Policy: Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia is considered in Blue Shield of California Medical Policy: Hematopoietic Cell Transplantation for Waldenström Macroglobulinemia.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
Reduced-intensity conditioning (RIC) would be considered an option in patients who meet criteria for allogeneic hematopoietic cell transplantation (HCT), but whose age (typically greater than 55 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy) preclude the 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 non-Hodgkin lymphoma 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
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 stem cells, whether or not there is evidence of persistent disease following the first treatment cycle. Sometimes, the second cycle may use nonmyeloablative immunosuppressive conditioning followed by infusion of allogeneic stem 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 (e.g., 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.

High-risk (aggressive) T-cell and natural killer cell neoplasms are a clinically heterogeneous group of rare disorders, most of which have an aggressive clinical course and poor prognosis. The exception includes the following subtypes, which typically have a relatively indolent and protracted course: T-cell large granulocyte leukemia, chronic lymphoproliferative disorder of natural killer cells, early-stage mycosis fungoides, primary cutaneous anaplastic large-cell lymphoma, and anaplastic lymphoma kinase-anaplastic large-cell lymphomas.

Description

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 [allo-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 Blue Shield of California Medical Policy: Placental and Umbilical Cord Blood as a Source of Stem Cells.

Related Policies

- Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
- Hematopoietic Cell Transplantation for Hodgkin Lymphoma
- Hematopoietic Cell Transplantation for Primary Amyloidosis

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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

Rationale

Background
Treatment for Non-Hodgkin Lymphoma

Hematopoietic Cell Transplantation
Hematopoietic cell transplantation (HCT) is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune 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 [allo-HCT]). These cells can be harvested from bone marrow, peripheral blood, or the umbilical cord blood shortly after delivery of neonates. Cord blood transplantation is discussed in detail in Blue Shield of California Medical Policy: Placental and Umbilical Cord Blood as a Source of Stem Cells.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allogeneic stem cell transplantation, immunologic compatibility between donor and patient is a critical factor for achieving a successful outcome. Compatibility is established by typing human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. An acceptable donor will match the patient at all or most of the HLA loci.

Conditioning for Hematopoietic Cell Transplantation
Conventional Conditioning
The conventional ("classical") practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of the initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease (GVHD), which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of the bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation
Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versusmalignancy effect of allogeneic transplantation develops. RIC regimens range from nearly

total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. In this review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and 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 technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 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. Randomized controlled trials 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Non-Hodgkin Lymphoma

A heterogeneous group of lymphoproliferative malignancies, non-Hodgkin lymphoma (NHL) usually originates in lymphoid tissue. Historically, the 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 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 2022 WHO classification (see Table 1).[4,]

Table 1. Updated World Health Organization Classification (2022)

Tumor-like lesions with B-cell predominance
Reactive B-cell-rich lymphoid proliferations that can mimic lymphoma[a]
IgG4-related disease[a]
Unicentric Castleman disease[a]
Idiopathic multicentric Castleman disease[a]
KSHV/HHV8-associated multicentric Castleman disease[a]
Precursor B-cell neoplasms
B-cell lymphoblastic leukaemias/lymphomas
B-lymphoblastic leukaemia/lymphoma, NOS
B-lymphoblastic leukaemia/lymphoma with high hyperdiploidy[a]
B-lymphoblastic leukaemia/lymphoma with hypodiploidy
B-lymphoblastic leukaemia/lymphoma with iAMP21
B-lymphoblastic leukaemia/lymphoma with BCR::ABL1 fusion[a]
B-lymphoblastic leukaemia/lymphoma with BCR::ABL1-like features[a]
B-lymphoblastic leukaemia/lymphoma with KMT2A rearrangement[a]
B-lymphoblastic leukaemia/lymphoma with ETV6::RUNX1 fusion[a]
B-lymphoblastic leukaemia/lymphoma with ETV6::RUNX1-like features[a]
B-lymphoblastic leukaemia/lymphoma with TCF3::PBX1 fusion[a]
B-lymphoblastic leukaemia/lymphoma with IGH::IL3 fusion[a]
B-lymphoblastic leukaemia/lymphoma with TCF3::HLF fusion[a]
B-lymphoblastic leukaemia/lymphoma with other defined genetic abnormalities
Mature B-cell neoplasms
Pre-neoplastic and neoplastic small lymphocytic proliferations
Monoclonal B-cell lymphocytosis
Chronic lymphocytic leukaemia/small lymphocytic lymphoma
Splenic B-cell lymphomas and leukaemias
Hairy cell leukaemia
Splenic marginal zone lymphoma
Splenic diffuse red pulp small B-cell lymphoma
Splenic B-cell lymphoma/leukaemia with prominent nucleoli[a]
Lymphoplasmacytic lymphoma
Lymphoplasmacytic lymphoma
Marginal zone lymphoma
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
Primary cutaneous marginal zone lymphoma[a]
Nodal marginal zone lymphoma
Paediatric marginal zone lymphoma
Follicular lymphoma
In situ follicular B-cell neoplasm[a]
Follicular lymphoma
Paediatric-type follicular lymphoma
Duodenal-type follicular lymphoma
Cutaneous follicle centre lymphoma
Primary cutaneous follicle centre lymphoma
Mantle cell lymphoma
In situ mantle cell neoplasm[a]
Mantle cell lymphoma
Leukaemic non-nodal mantle cell lymphoma
Transformations of indolent B-cell lymphomas
Transformations of indolent B-cell lymphomas[a]
Large B-cell lymphomas
Diffuse large B-cell lymphoma, NOS
T-cell/histiocyte-rich large B-cell lymphoma
Diffuse large B-cell lymphoma/ high grade B-cell lymphoma with MYC and BCL2 rearrangements[a]
ALK-positive large B-cell lymphoma
Large B-cell lymphoma with IRF4 rearrangement
High-grade B-cell lymphoma with 11q aberrations[a]
Lymphomatoid granulomatosis

Tumor-like lesions with B-cell predominance
EBV-positive diffuse large B-cell lymphoma[a]
Diffuse large B-cell lymphoma associated with chronic inflammation
Fibrin-associated large B-cell lymphoma[a]
Fluid overload-associated large B-cell lymphoma[a]
Plasmablastic lymphoma
Primary large B-cell lymphoma of immune-privileged sites[a]
Primary cutaneous diffuse large B-cell lymphoma, leg type
Intravascular large B-cell lymphoma
Primary mediastinal large B-cell lymphoma
Mediastinal grey zone lymphoma[a]
High-grade B-cell lymphoma, NOS
Burkitt lymphoma
Burkitt lymphoma
KSHV/HHV8-associated B-cell lymphoid proliferations and lymphomas
Primary effusion lymphoma
KSHV/HHV8-positive diffuse large B-cell lymphoma[a]
KSHV/HHV8-positive germinotropic lymphoproliferative disorder[a]
Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation
Hyperplasias arising in immune deficiency/dysregulation[a]
Polymorphic lymphoproliferative disorders arising in immune deficiency/dysregulation[a]
EBV-positive mucocutaneous ulcer
Lymphomas arising in immune deficiency / dysregulation[a]
Inborn error of immunity-associated lymphoid proliferations and lymphomas[a]
Hodgkin lymphoma
Classic Hodgkin lymphoma
Nodular lymphocyte predominant Hodgkin lymphoma
Plasma cell neoplasms and other diseases with paraproteins
Monoclonal gammopathies
Cold agglutinin disease[a]
IgM monoclonal gammopathy of undetermined significance
Non-IgM monoclonal gammopathy of undetermined significance
Monoclonal gammopathy of renal significance[a]
Diseases with monoclonal immunoglobulin deposition
Immunoglobulin-related (AL) amyloidosis[a]
Monoclonal immunoglobulin deposition disease[a]
Heavy chain diseases
Mu heavy chain disease
Gamma heavy chain disease
Alpha heavy chain disease
Plasma cell neoplasms
Plasmacytoma
Plasma cell myeloma
Plasma cell neoplasms with associated paraneoplastic syndrome[a]
POEMS syndrome
TEMPI syndrome
AESOP syndrome

[a]Changes from 2016 WHO classification.

AESOP: adenopathy and extensive skin patch overlying a plasmacytoma; ALK: anaplastic lymphoma kinase; EBV: Epstein-Barr virus; HHV: human herpes virus; KSHV: Kaposi's sarcoma-associated herpesvirus; NOS: not otherwise specified; POEMS: polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes; TEMPI: telangiectasias, elevated erythropoietin level and erythrocytosis, monoclonal gammopathy, perinephric fluid collections, and intrapulmonary shunting.

In the United States, B-cell lymphomas represent approximately 85% of cases of NHL, and T-cell lymphomas represent approximately 15%.[5,]Natural killer lymphomas are relatively rare.[1,]
The International Lymphoma Classification Project identified the most common NHL subtypes as follows: diffuse large B-cell lymphoma (DLBCL) 31%, follicular lymphoma (FL) 22%, small lymphocytic

lymphoma and chronic lymphocytic leukemia 6%, MCL 6%, PTCL 6%, and marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue lymphoma 5%. All other subtypes each represent fewer than 2% of cases of NHL.[1,]

Types of Non-Hodgkin Lymphoma

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.[1,] 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 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% to 80% of cases), and often the terms indolent lymphoma and FL 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.

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

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 the 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 FL, which has multiple independent risk factors for relapse after first complete remission (CR). 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 5 factors are used to stratify patients into 3 categories of risk: low (0 to 1 risk factor), intermediate (2 risk factors), or poor (3 or more risk factors).[8,]

Indolent B-Cell Lymphomas

Clinical Context and Therapy Purpose

The purpose of autologous hematopoietic cell transplantation (HCT) as first-line therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with indolent B-cell NHLs.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with indolent B-cell NHLs.

Interventions

The therapy being considered is autologous HCT as first-line therapy.

Comparators

Comparators of interest include standard of care.

Outcomes

The general outcomes of interest are OS, disease-specific survival (DSS), change in disease status, morbid events, treatment-related mortality, and treatment-related morbidity. Follow-up over years is of interest for relevant outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Hematopoietic Cell Transplantation as First-Line Treatment for Indolent Non-Hodgkin Lymphomas

Systematic Reviews

Al Khabori et al (2012) performed a systematic review and meta-analysis of the use of autologous HCT in untreated, advanced FL.[9,] Four RCTs comparing autologous HCT with conventional chemotherapy (N=941) were included. Three trials reported 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.

Schaaf et al (2012) 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.[10,] Five RCTs involving 1093 patients were included, with 4 trials in previously untreated patients and 1 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<.001). However, there was no statistically significant OS advantage (HR, 0.97; 95% CI, 0.76 to 1.24; p=.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 mortality (relative risk [RR], 1.28; 95% CI, 0.25 to 6.61; p=.77), secondary acute myeloid leukemia/myelodysplastic syndromes (RR, 2.87; 95% CI, 0.7 to 11.75; p=.14), or solid cancers (RR, 1.20; 95% CI, 0.25 to 5.77; p=.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

Ladetto et al (2008) reported on the results of a phase 3, randomized, multicenter trial of patients with high-risk FL, treated at diagnosis.[11,] 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. The rate of 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.

Sebban et al (2006) reported on the results of a randomized, multicenter study.[12,] 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=.53) or EFS (p=.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.[13,] 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.

Lenz et al (2004) reported on the results of a trial of 307 patients with advanced-stage lymphoma in first remission, including FL, MCL, or lymphoplasmacytoid lymphoma.[14,] Patients were randomized to consolidative therapy plus autologous HCT or interferon therapy. The 5-year PFS rate was considerably 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.

Hematopoietic Cell Transplantation for Relapsed or Refractory, Indolent Non-Hodgkin Lymphomas

Randomized Controlled Trial

In most patients with FL relapse, and with relapsed disease, a cure is unlikely, with a median survival of 4.5 years after recurrence.[15,] 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).[14,] OS rates at 4 years for chemotherapy versus unpurged versus 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 (DFS) with autologous HCT for relapsed FL, this study was the first to show a difference in OS benefit.

Observational Studies

A single-center retrospective study by Bozkaya et al (2017) analyzed data from 38 patients who were treated between 2004 and 2014 with high-dose chemotherapy followed by autologous HCT.[16,] 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 versus 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 the 5-year OS rate was significantly higher for chemosensitive patients (50%) than for chemoresistant patients (22%; p=.02); however, given the small size of the population, other analyses were primarily descriptive or showed no statistical significance.

Jiménez-Ubieto et al (2018) analyzed the GELTAMO (Grupo Español de Linfomas y Trasplantes de Médula Ósea) registry to evaluate the effectiveness of autologous stem cell transplant (ASCT) for patients with FL who experience early therapy failure (ETF) within 2 years of frontline immunochemotherapy.[17,] The analysis included patients with non-transformed FL treated with rituximab. ETF was defined as relapse or progression within 2 years of first-line therapy. Two groups were studied: the ETF group (n=52; 38 receiving ASCT in second complete response [CR2] and 14 in second partial response [PR2]) and the non-ETF group (n=16; 14 patients receiving ASCT in CR2 and 2 in PR2, but who did not experience ETF). No significant difference was found between the ETF and non-ETF groups in 5-year PFS (49% vs. 60%, respectively; p=.49) or 5-year OS (81% vs. 83%, p=.8). The authors also found that patients in the ETF cohort who underwent ASCT in CR showed a plateau in the PFS curves beyond 7 years of follow-up at 50%. The authors concluded that because patients

with FL who experience ETF after frontline therapy have few treatment options, ASCT may be an early consolidation option for those patients who respond to rescue treatments.

Section Summary: Indolent B-Cell Lymphomas

For individuals who have indolent B-cell non-Hodgkin lymphomas (NHL) who receive autologous HCT as first-line therapy, the evidence includes observational studies, RCTs, and systematic reviews. 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. Observational studies have shown similar results.

Aggressive B-Cell Lymphomas

Clinical Context and Therapy Purpose

The purpose of autologous HCT as consolidation therapy after first CR is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with aggressive B-cell NHLs, excluding MCL.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with aggressive B-cell NHLs, excluding MCL.

Interventions

The therapy being considered is autologous HCT as consolidation therapy after first CR.

Comparators

Comparators of interest include standard of care.

Outcomes

The general outcomes of interest are OS, DSS, change in disease status, morbid events, treatment-related mortality, and treatment-related morbidity. Follow-up over years is of interest for relevant outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Hematopoietic Cell Transplantation for First-Line Therapy for Aggressive Non-Hodgkin Lymphomas

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.[18,] Fifteen RCTs (N=3079) were eligible for the meta-analysis. Thirteen studies (n=2018 patients) showed significantly higher CR rates in the autologous HCT group (p=.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

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.[19,20,21,22,] As summarized in a 2002 editorial, the preponderance of evidence showed that consolidating first CRs with HCT did not improve OS for the full population of enrolled patients.[23,] 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, Survival Benefit of High-Dose Therapy in Poor-Risk Aggressive Non-Hodgkin's Lymphoma: Final Analysis of the Prospective LNH87-2 Protocol (LNH87-2 protocol).[24,] The subgroup analysis reported superior OS (64% vs. 49%, respectively; RR, 1.51, p=.04) and DFS (55% vs. 39%, respectively; RR, 1.56, p=.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, Autologous Transplantation as Consolidation in Aggressive Lymphoma (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[25,] 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 [23,25,] and reviews[26,27,28,] 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).

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.[29,] 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=.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.[30,] The 5-year actutimes OS and PFS rates did not differ statistically between the 2 study groups; only DFS differed statistically (97% for the autologous HCT group vs. 47% for the conventional group; p=.02.)

Olivieri et al (2005) reported on a randomized study of 223 patients with aggressive NHL using upfront high-dose chemotherapy plus autologous HCT versus conventional chemotherapy plus autologous HCT in cases of failure.[31,] 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=.5), DFS (62% and 71%, p=.2), or PFS (44.9% and 40.9%, p=.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, Chemoradiotherapy and Peripheral Stem Cell Transplantation Compared With Combination Chemotherapy in Treating Patients With Non-Hodgkin's Lymphoma (SWOG-9704) of autologous HCT as consolidation for aggressive (high-intermediate or high-risk) diffuse B-cell NHL were published in 2013.[32,] 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 endpoints of the trial were 2-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=.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=.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=.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 phase 2 clinical trial, A Study of Two Associations of Rituximab and Chemotherapy, With a PET-driven Strategy, in Lymphoma (LNH2007-3B) by Casasnovas et al (2017) 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.[33,] 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 endpoint, 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% of R-CHOP14 patients (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=.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<.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.

Observational Studies

A single-center cohort study by Strüssmann et al (2017) 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.[34,] All patients had an age-adjusted IPI score of 2 or 3, and demographic information was comparable for both cohorts (e.g., 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=.009), a finding was also

statistically significant in multivariate analysis (HR, 8.12; 95% CI, 1.73 to 36; p=.006). The OS rate at 2 years was 69.7% for cohort 1 and 93.3% for cohort 2 (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 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.

Qualls et al (2017) published a small retrospective study of 20 individuals (13 men, 7 women) treated with autologous HCT for systemic NHL with some form of central nervous system (CNS) involvement.[35], 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 the first CR. Progression-free survival rates were high at 1-year (84%; 95% CI, 59% to 95%) and 4-year (77%; 95% CI, 48% to 91%) follow-ups. The OS rates were similarly high at 1 year (95%; 95% CI, 68% to 99%) and 4 years (82%; 95% CI, 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 rarity of CNS involvement among patients with NHL, suggesting that the high survival rates observed in the study supported the use of autologous HCT in the first CR.

Hematopoietic Cell Transplantation for Relapsed, Aggressive Non-Hodgkin Lymphomas

Randomized Controlled Trials

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.[1,36,] The pivotal trial that established the superiority of autologous HCT for relapsed DLBCL is the Autologous Bone Marrow Transplantation as Compared with Salvage Chemotherapy in Relapses of Chemotherapy-Sensitive Non-Hodgkin's Lymphoma ([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.[37,] 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=.001); the OS rate was 53% in the transplant group and 32% in the nontransplant group (p=.038).

Observational Study

Using the national registry of hematopoietic stem cell transplantation in Japan, Fujita et al (2019) conducted a retrospective study on the effect of allogeneic or autologous HCT in children and adolescents (<18 years old) with relapsed or refractory B-cell non-Hodgkin lymphoma.[38,] They analyzed 5-year survival rates for 31 autologous HCTs and 48 allo- HCTs and found that with any HCT, the rate was 41% (95% CI, 30% to 52%). When data on the 2 types of HCT were separated, autologous HCT had a significantly higher survival rate than allo-HCT (55% [95% CI, 36% to 70%] vs. 32% [95% CI, 18% to 46%]; p=.036). Factors for poor prognosis included allogeneic graft, Burkitt histology, and lack of response to chemotherapy. Better survival was associated with positive response to chemotherapy before HCT, autologous graft, and diffuse large B-cell histology. In addition, treatment-related mortality was significantly higher with allo-HCT than with autologous HCT (23% [95% CI, 12% to 35%] vs. 3.2% [95% CI, 2.4% to 14%]; p=.017). For relapse, no statistically significant difference was found between allo-HCT and autologous HCT.

Section Summary: Aggressive B-Cell Lymphomas

For individuals who have aggressive B-cell NHL, excluding mantle cell lymphoma (MCL), who receive autologous HCT as consolidation therapy after first CR, the evidence includes RCTs and a systematic review. 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 CR. Randomized studies of HCT for relapsed aggressive B-cell lymphomas have also shown an OS benefit with the previously described approach. Results of a retrospective study comparing autologous and allo-HCT for relapsed or refractory B-cell NHL showed more positive outcomes for autologous HCTs.

Tandem Autologous and Allogeneic Transplants

Clinical Context and Therapy Purpose

The purpose of tandem autologous and allo-HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with NHLs, excluding MCL.
The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with NHLs, excluding MCL.

Interventions

The therapy being considered is tandem autologous and allo-HCT.

Comparators

Comparators of interest include standard of care.

Outcomes

The general outcomes of interest are OS, DSS, change in disease status, morbid events, treatment-related mortality, and treatment-related morbidity. Follow-up over years is of interest for relevant outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Nonrandomized Studies

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.[39], After induction, responders underwent tandem autologous transplantation; 31 of 41 evaluable patients completed the program. There were 4 toxicity-related deaths. The primary endpoint of the trial was the 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.[40,] 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.

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.[41,] 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.

Stiff et al (2013) conducted a retrospective analysis of 34 high-risk NHL patients who underwent autologous HCT followed closely by reduced-intensity conditioning (RIC) allo-HCT in patients treated from 2002 to 2010.[32,] 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 HLA-identical donor, but further study is necessary to establish its role in this setting.

Satwani et al (2015) conducted a non-randomized study on the sequential combination of myeloablative therapy and autologous stem cell transplantation followed by reduced-intensity allo-HCT and post-HCT adoptive cellular immunotherapy for refractory or recurrent NHL and Hodgkin's Disease.[42,] The participants were divided into 2 arms: Arm A received allogeneic stem cells from a family member (n=6), and Arm B received stem cells from an unrelated donor (n=17). All participants were followed for 1 year after treatment. A complete response was seen in 66.7% of Arm A and 70.6% in Arm B. Disease relapse or progression was experienced by 16.7% of Arm A and 17.6% of Arm B. Partial response or stable disease was seen in 66.7% of Arm A and 52.9% of Arm B. Two participants (33.3%) in Arm A and 6 (35.3%) in Arm B died of transplant-related causes by the 1-year follow-up.

Section Summary: Tandem Autologous and Allogeneic Transplants

For individuals who have NHL, excluding MCL, who receive tandem autologous and allo-HCT, the evidence includes several nonrandomized trials. 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.

Non-Hodgkin Lymphoma Subtypes

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

Autologous, Allogeneic, or Tandem Transplant for 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).[43,] 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

A prognostic index has recently 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.[44,] 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.

- Age
- ECOG Performance Status
- Serum LDH (calculated as a ratio of LDH to a laboratory's upper limit of normal)
- White blood cell (WBC) count
    - 0 points each are assigned to age younger than 50 years, ECOG Performance Status score of 0 to 1, LDH ratio of less than 0.67 U/L, WBC of less than 6700/mL
    - 1 point each for age 50 to 59 years, LDH ratio of 0.67 to 0.99 U/L, WBC of 6700 to 9999/mL
    - 2 points each for age 60 to 69 years, ECOG Performance Status score of 2 to 4, LDH ratio of 1.00 to 1.49 U/L, WBC of 10000 to 14999/mL
    - 3 points each for age 70 years or older, LDH ratio of 1.5 U/L or greater, WBC of 15000/mL or more.

MCL IPI allows separation of 3 groups with significantly different prognoses[44,]:

- 0 to 3 points denote low-risk, which affects 44% of patients, who have a 5-year OS rate of 60% (median OS, not reached)
- 4 to 5 points denote intermediate risk, which affects 35% of patients, who have a median OS of 51 months
- 6 to 11 points denote high-risk, which affects 21% of patients, who have a median OS of 29 months

Clinical Context and Therapy Purpose

The purpose of autologous, allogeneic, or tandem HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with MCL.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with MCL.

Interventions

The therapy being considered is autologous, allogeneic, or tandem HCT.

Comparators

Comparators of interest include standard of care.

Outcomes
The general outcomes of interest are OS, DSS, change in disease status, morbid events, treatment-related mortality, and treatment-related morbidity. Follow-up over years is of interest for relevant outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Autologous Hematopoietic Cell Transplantation
To improve outcomes of MCL, several phase 2 trials have investigated the efficacy of autologous HCT, with published results differing substantially.[44,45,] Some studies found no benefit to HCT, and others suggested an EFS advantage, at least in a subset of patients.[44,] The differing results were likely due to different time points of transplant (first vs. second remission) and patient selection criteria.[45,] The results of the first randomized trial were reported by Dreyling et al (2005) of the European MCL Network.[45,] 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 of 37% with interferon). Survival curves for time to treatment failure after randomization showed that autologous HCT was superior to interferon (p=.003). There was also a significant improvement in the 3-year PFS rate in the autologous HCT arm (54%) versus the interferon arm (25%; p=.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).[46,]The 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 the relapsed or refractory disease was 6.1 times that of patients transplanted in first CR or PR (p<.001).

Geisler et al (2008) reported on 160 previously untreated patients with MCL with dose-intensified induction immunochemotherapy.[47,] Responders received high-dose chemotherapy with in vivo purged autologous HCT. The 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%.[48,] 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 retrospective case series of 268 patients drawn from the GELTAMO registry and 35 hospitals in Spain, García-Noblejas et al (2017) evaluated the response of individuals with MCL to autologous HCT as first-line treatment.[49,] 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=.01). There was a similar association between first CR status and OS, compared with other statuses: 97 months versus 57 months (p=.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=.015 vs. RR for OS, 0.8 [95% CI, 1.2 to 2.7], p=.003). During univariate analysis, prior exposure to rituximab was associated with a greater PFS and OS (respectively, p=.02; p<.001); however, this association was not 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 (e.g., PR or 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.

Zoellner et al (2021) conducted a post-hoc analysis of an open-label, multicenter, randomized phase 3 trial on previously untreated MCL patients.[50,] A total of 269 patients were randomized to receive myeloablative radiochemotherapy followed by autologous HCT (n=134) or interferon alfa maintenance after completion of a CHOP-like induction therapy (n=135) with or without rituximab. The median follow-up period was 14 years, with the intention-to-treat population consisting of 174 patients (93 in the autologous HCT group and 81 in the interferon alfa maintenance group) who responded to induction therapy. The median PFS in the autologous HCT group was 3.3 years (95% CI, 2.5 to 4.3 years) compared to 1.5 years (95% CI, 1.2 to 2.0 years) in the interferon alfa group (log-rank p<.0001; adjusted HR, 0.5 [95% CI, 0.36-0.69]). The median OS in the autologous HCT group was 7.5 years (95% CI, 5.7 to 12.0 years) and 4.8 years (95% CI, 4.0 to 6.6 years) in the interferon alfa group (log-rank p=.019; adjusted HR, 0.66 [95% CI, 0.46-0.95]). For patients treated with a rituximab-containing induction regimen, neither PFS nor OS was significantly different between the 2 groups.

Allogeneic Hematopoietic Cell Transplantation

Several studies have assessed allo-HCT in patients with MCL.[51,] 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 actutimes probability of EFS was 82% at 3 years.[52,] 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.[53,]Krüger et al (2021) conducted 2 prospective trials for de novo MCL (n= 24) and for relapsed or refractory MCL (n=15) treated with allo-HCT. [54,]Patients with de novo MCL had to have at least a PR before proceeding to allo-HCT; de novo MCL patients had a median OS and PFS after transplantation of 5.4 years (range, 0.02 to 16.5 years) and 5.2 years (range, 0.02 to 16.5 years) respectively. Relapsed or refractory MCL patients had a median OS and PFS of 8.5 years (range, 0.02 to 14.8 years) and 7.9 years (range, 0.02 to 14.8 years), respectively.

Tandem Autologous Hematopoietic Cell Transplantation and Allogeneic Hematopoietic Cell Transplantation

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.[55,] 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 (e.g., CHOP-R). For patients with relapsed or primary refractory MCL, autologous HCT was performed before the use of nonmyeloablative allogeneic HCT in 1997. After 1997, nonmyeloablative allogeneic HCT was performed whenever a histocompatible donor was available. Patients generally underwent autologous HCT up to the age of 70 years 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 actutimes 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 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 actutimes 6-year PFS and OS rates were 10% and 35%, respectively (p=.01 and 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 actutimes PFS rate was 46%, and the 6-year actutimes 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=.01 for PFS; p=.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 HCT patients.

This study provided evidence that MCL may be curable in both the first-line and salvage settings. In chemotherapy-naive 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 a salvaging treatment option for patients no longer curable with maximum cytotoxic strategies.

As noted in the Tam et al (2009) study,[55,] 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.[44,56,] 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.[56,]

Section Summary: Autologous, Allogeneic, or Tandem Transplant for Mantle Cell Lymphoma
For individuals who have MCL who receive autologous, allogeneic, or tandem HCT, the evidence includes case series and RCTs. Case series and RCTs 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.

Autologous or Allogeneic Transplant for Peripheral T-Cell Lymphoma (Mature T-Cell or Natural Killer Cell Neoplasms)
Most PTCLs are aggressive and fall into the category of PTCL, unspecified PTCL, or PTCL not otherwise specified, 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.

Clinical Context and Therapy Purpose
The purpose of autologous or allo- HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with PTCL.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with PTCL.

Interventions
The therapy being considered is autologous or allo-HCT.

Comparators
Comparators of interest include standard of care.

Outcomes
The general outcomes of interest are OS, DSS, change in disease status, morbid events, treatment-related mortality, and treatment-related morbidity. Follow-up over years is of interest for relevant outcomes

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

First-Line Autologous Hematopoietic Cell Transplantation for Peripheral T-Cell Lymphoma

Systematic Review

Zhai et al (2022) published a meta-analysis including 12 studies (N=1617) that compared the efficacy of conventional chemotherapy versus high-dose chemotherapy plus consolidation with autologous HCT as the first-line therapy for adults with nodal PTCL.[57,] The results showed that individuals who received autologous HCT as the first-line consolidation therapy had improved OS at 3 years (OR, 0.58; 95% CI, 0.30 to 1.13), which reached statistical significance at 5 years (OR, 0.73; 95% CI, 0.55 to 0.96). Furthermore, individuals who received autologous HCT had statistically significantly prolonged PFS at 3 years (OR, 0.41; 95% CI, 0.21 to 0.80) and 5 years (OR, 0.55; 95% CI, 0.39 to 0.75).

Randomized Controlled Trial

Schmitz et al (2021) conducted a randomized, prospective phase 3 trial of autologous versus allo-HCT as part of first-line therapy in patients with PTCL. [58,]There were 104 patients enrolled, age 18 to 60 years, who were randomized to 4 cycles of CHOP without etoposide (CHOEP) and 1 cycle of dexamethasone, cytosine-arabinoside, and platinum (DHAP) followed by high-dose therapy and autologous HCT (n=54) or myeloablative conditioning and allo-HCT (n=49). A few study patients were unable to proceed with transplantation due to disease progression, toxicity, or other reasons, so the final patient population consisted of 41 patients who underwent autologous HCT and 26 patients who underwent allo-HCT. The median follow-up period was 42 months and the 3-year EFS was 38% (95% CI, 25% to 52%) in the autologous HCT group versus 43% (95% CI, 29% to 57%) in the allo-HCT group. The 3-year OS was 70% (95% CI, 57% to 82 %) in the autologous HCT group versus 57% (95% CI, 43% to 71%) in the allo-HCT group.

Observational Cohort Studies

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.[59,] 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.[60,] In an intention-to-treat analysis, 46 (74%) of the 62 completed the whole program. Sixteen patients failed to undergo transplants 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 the 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<.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).[61,] 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 outcomes in patients responding to induction therapy.[62,] 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.

Wang et al (2018) conducted a retrospective study to investigate the efficacy of HCT in treating extranodal natural killer/T-cell lymphoma. Researchers compared 20 patients from a single-center who received the treatment followed by radiotherapy and chemotherapy with 60 additional patients who received chemotherapy and radiotherapy without HCT. The analysis found that 5-year OS was 79.3% for the HCT group compared with 52.3% for the control group (p=.026). Limitations included the retrospective design, lack of multiple centers, and small sample size.[63,]

First-Line Allogeneic Hematopoietic Cell Transplantation for Peripheral T-Cell Lymphoma

Kewalramani et al (2006) reviewed the impact of HCT in PTCLs and found no relevant data on the use of allo-HCT in the front-line setting.[64,] 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.[59,]

Mamez et al (2020) conducted a retrospective, registry-based analysis from 32 centers in Europe (mainly France) to assess survival outcomes among 285 patients with PTCL treated with allo-HCT.[65,] Included patients had PTCL subtypes of PTCL-NOS (n=110), angioimmunoblastic T lymphomas (n=83), ALCL (n=43), Natural Killer/T lymphoma nasal type (n=16), HSTL (n=12), EATL (n=3), T large granular lymphocytic leukemia (n=1), and Natural Killer leukemia (n=1). Allo-HCT was performed as a part of front-line therapy in 138 patients (n=93 in their first CR and n=45 in their first PR), and as salvage therapy or second-line consolidation therapy in relapsed/progressive disease, which is further described later in this review. Among patients who received allo-HCT as part of front-line therapy, 2-year OS was 66% (95% CI, 0.58 to 0.74) and 4-year OS was 63% (95% CI, 0.53 to 0.70). At 2 years, the cumulative incidence of relapse was 19% (95% CI, 0.12 to 0.25). Transplant-related mortality was 23% (95% CI, 0.15 to 0.31) at 2 years and 24% (95% CI, 0.17 to 0.32) at 4 years, and graft versus host disease-free relapse-free survival (defined as the first occurrence of death, progression/relapse, grade 3 to 4 acute graft versus host disease, or extensive chronic graft versus host disease after allo-HCT) was 48% (95% CI, 0.39 to 0.56) at 2 years.

Salvage Allogeneic or Autologous Hematopoietic Cell Transplantation (Relapsed or Refractory Peripheral T-Cell Lymphoma)

Systematic Reviews

Du et al (2021) conducted a systematic review and meta-analysis to compare the effectiveness and safety of autologous HCT versus allo-HCT in patients with refractory or relapsed PTCL.[66,] The review was performed for studies from 2001 to 2020, and there were 30 studies included (N=1765) with patients undergoing allo-HCT (n=880) and autologous HCT (n=885). For patients in the autologous HCT group, the combined 3-year OS, PFS, and transplant-related mortality were 55% (95% CI, 48% to 64%), 41% (95% CI, 33% to 51%), and 7% (95% CI, 2% to 23%), respectively; the combined 5-year OS and PFS were 53% (95% CI, 44% to 64%) and 40% (95% CI, 24% to 58%), respectively. For patients in

the allo-HCT group, the combined 3-year OS, PFS, and transplant-related mortality were 50% (95% CI, 41% to 60%), 42% (95% CI, 35% to 51%), and 32% (95% CI, 27% to 37%), respectively; the combined 5-year OS and PFS were 54% (95% CI, 47% to 62%) and 48% (95% CI, 40% to 56%), respectively. The findings in this review suggest that overall HCT is an effective therapy for patients with refractory or relapsed PTCL, however autologous HCT may be a safer option in this patient population. A limitation to note is that most of the eligible studies included were single-arm trials, and so results could not directly be compared.

Randomized Control Trials

The RCTs not included within the Du et al (2021) systematic review and meta-analysis are summarized below.

Salvage Autologous Hematopoietic Cell Transplantation (Relapsed or Refractory Peripheral T-Cell Lymphoma)

Song et al (2003) compared the outcomes of 36 patients who had PTCL who underwent autologous HCT with 97 patients who had relapsed DLBCL.[67,] Of patients with PTCL, 27 were at first relapse, 2 at greater than 1 relapse, and 7 had primary refractory disease. Twenty patients had unspecified PTCL, 9 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=.41 and.29, respectively). The patients with unspecified PTCL had an inferior EFS rate when compared with the DLBCL patients (23%, p=.028), and those with ALCL had a nonsignificant trend for improved EFS (67%, p=.41).

Rodriguez et al (2007) reported on the largest series of patients with refractory or relapsed PTCL who received an autologous HCT.[68,] 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%).

Salvage Allogeneic Hematopoietic Cell Transplantation (Relapsed or Refractory Peripheral T-Cell Lymphoma)

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 10 patients.[59,]
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.[69,] 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 conditioning and 20 underwent 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.

Section Summary: Autologous or Allogeneic Transplant for Peripheral T-Cell Lymphoma (Mature T-Cell or Natural Killer Cell Neoplasms)

For individuals who have peripheral T-cell lymphoma (PTCL) who receive autologous or allo-HCT, the evidence mainly includes prospective trials and case reports/series. 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: 1 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). For first-line therapy, autologous and allo-HCT were compared in a phase 3 trial, and there were comparable OS and PFS rates between the two groups. Results from recent phase 2 studies with autologous HCT as consolidation offers the best survival outcomes for patients with high-risk features; RCTs to confirm this have not been performed. A single retrospective registry study showed a potential survival benefit among patients treated with allo-HCT in the front-line setting; however, prospective studies are not available. Similarly, high-dose chemothearpy plus consolidation with autologous HCT as the first-line therapy for adults with nodal PTCL demonstrated improved OS and PFS in a systematic review. 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.

Autologous or Allogeneic Transplant for Hepatosplenic T-cell Lymphoma

Hepatosplenic T-cell Lymphoma (HSTCL) is a rare subtype of PTCL, with an aggressive clinical course.The median OS ranges from 3 to 28 months and the 5-year OS rate is less than 15%. It occurs predominantly in young adult males (median age of 35 years).The estimated incidence of HSTCL in the U.S. is 15.2 cases per one million people. HSTCL has been underrepresented in prospective clinical studies and treatment recommendations are primarily derived from small case reports or case series and single-center retrospective studies. [70,]

Clinical Context and Therapy Purpose

The purpose of autologous or allo- HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with hepatosplenic T-cell Lymphoma (HSTCL) after first response (complete or partial) to induction chemotherapy.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with HSTCL after first response (complete or partial) to induction chemotherapy.

Interventions

The therapy being considered is autologous or allo-HCT as consolidation therapy.

Comparators

Comparators of interest include standard of care without allo-HCT. The preferred standard of care chemotherapy regimen is ICE (ifosfamide, carboplatin, and etoposide). Other recommended regimens include DHA (dexamethasone and cytarabine) plus a platinum agent (carboplatin, cisplatin, or oxaliplatin); dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin); HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine; or IVAC (ifosfamide, etoposide, and cytarabine).

While up to half of patients may achieve a CR with chemotherapy, remissions are typically short lived with a median OS of approximately one year. Long-term remission is primarily or exclusively seen in those who have undergone consolidative HCT.[70,]

Outcomes

The general outcomes of interest are OS, DSS, change in disease status, morbid events, treatment-related mortality, and treatment-related morbidity. Follow-up over years is of interest for relevant outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Two patient-level meta-analyses evaluated autologous or allo-HCT in individuals with HSTCL. The characteristics of the meta-analyses are provided in Table 3. Klebaner et al (2020) compared response rates and survival among patients who received non-CHOP-based induction with regimens containing cytarabine, etoposide, and/or platinum-based treatment to those receiving treatment with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOP-like therapy.[71,] Consolidation with autologous HCT or allo-HCT was done in 21 and 15 patients, respectively. Rashidi et al (2015) reported outcomes for patients with HSTCL who received allo-HCT (N=54).[72,] The conditioning was myeloablative in 70% of patients and RIT in 30%, but the specific chemotherapy regimens were not mentioned.

Table 3. Systematic Review & Meta-analysis Characteristics in Hepatosplenic T-cell Lymphoma

Study	Dates	Patients	Participants	Design	Duration
Klebaner et al (2020)[71,]	1990 to 2018	166	Patients with HSTCL who received CHOP/CHOP-like regimens or non-CHOP-based regimen, with or without HCT (allo-, n=15; autologous, n=21)	Individual-level meta-analyses	NR
Rashidi et al (2015)[72,]	Through March 2015	54	Patients with HSTCL who received allo-HCT	Individual-level meta-analyses	NR

CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; HCT: hematopoietic cell transplantation; HSTCL: hepatosplenic T-cell lymphoma; NR: not reported.

Results from both meta-analyses for patients who received HCT are presented in Table 4. Additionally, Klebaner et al (2020) found that survival was comparable among patients receiving non-CHOP-based therapy plus HCT versus non-CHOP-based therapy alone (35 vs. 38 months, respectively), followed by CHOP therapy plus HCT (25 months), and CHOP therapy alone (18 months). Furthermore, the association between non-CHOP-based treatment and improved survival persisted after adjustment for receipt of HCT (HR, 0.38; p=.0016).

Table 4. Systematic Review & Meta-analysis Results in Hepatosplenic T-cell Lymphoma

Study	Median OS (standard error)	2-year OS	3-year OS	RFS	3-year RFS
Klebaner et al (2020)[71,]					
No transplant	18 months	12%			
Allo-HCT	33 months	56%			
Autologous HCT	27 months	41%			
p-value	allo-HCT vs. autologous HCT: =.016	NR			
Rashidi et al (2015)[72,]					
Total N	42		42	44	44
Median (standard error)	18 (5) months		NA	68 (34) months	NA
Proportion	NA		56%	NR	42%

HCT: hematopoietic cell transplantation; MA: meta-analysis; NA: not applicable; NR: not reported; OS: overall survival; RFS: relapse-free survival; SR: systematic review.

Observational studies

Voss et al (2012) conducted a single-center, retrospective chart review of 14 patients who underwent treatment for HSTCL between 1994 and 2012.[73,] At the time of the report, 7 of 14 patients were alive, 3 to 149 months from the time of diagnosis (median follow-up, 65.6 months). All 7 surviving patients were treated with high-dose chemotherapy and consolidation HCT, and 6 of these 7 patients received non-CHOP induction therapy. After autologous HCT, 2 of 4 patients relapsed at 5 and 35 months; after allo-HCT, 2 of 7 patients relapsed at 3 and 6 months. One patient who received allo-HCT and one who received autologous HCT died of treatment-related toxicities.

Tanase et al (2015) published a registry-based retrospective study including 25 adults with HSTCL who underwent allo-HCT (n=18) or autologous HCT (n=7) between January 2003 and December 2011 and were reported to the European Society for Bone and Marrow Transplantation (EBMT) registry.[74,]After a median follow-up of 36 months, 9 patients (50%) were alive after allo-HCT (1 after relapse). The 3-year OS and PFS were 54% and 48%, respectively. After autologous HCT, 5 patients relapsed and subsequently died, 1 patient was lost to follow up 2 years after HCT, and 1 patient was alive and progression-free 58 months after HCT.

Section Summary: Autologous or Allogeneic Transplant for Hepatosplenic T-cell Lymphoma

Two meta-analyses using patient-level data found that consolidation therapy with HCT improves survival in patients with HSTCL. Two small, retrospective studies have shown similar results. Generally, outcomes are improved when non-CHOP regimens are used for induction therapy.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2011 Input

In response to requests, input was received from 3 physician specialty societies and 3 academic medical centers while this policy was under review in 2011. Input was solicited particularly for the use of hematopoietic cell transplantation (HCT) in mantle cell lymphoma (MCL) and peripheral T-cell

lymphoma. There was a uniform agreement for the use of autologous HCT to consolidate the first remission in MCL. There was a general agreement for the use of allogeneic HCT as salvage therapy for MCL, with less agreement on the use of autologous HCT in the salvage setting. For peripheral T-cell lymphoma, there was general agreement on the use of autologous HCT to consolidate a complete remission in high-risk patients and the salvage setting. Input was split on the use of allogeneic HCT to consolidate a first complete remission or as salvage therapy, but there was more support to consider it medically necessary in both settings.

2009 Input

In response to requests, input was received from 1 physician specialty society and 1 academic medical center while this policy was under review in 2009. There was general agreement with the policy statements. Both reviewers agreed that allogeneic HCT with reduced-intensity conditioning should be considered medically necessary in patients with non-Hodgkin lymphoma who do not qualify for a myeloablative allogeneic HCT. One reviewer responded on the medical necessity of HCT in patients with MCL in the first remission and recently published literature supported this. There was conflicting input on whether HCT should be considered investigational for peripheral T-cell lymphoma. Also, the 1 reviewer commented that with the increasing use of rituximab and its success in improving patient outcomes, the role of HCT in consolidating first complete response in high-risk patients is coming into question.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network (NCCN) guidelines on B-cell lymphomas (v.5.2022) include the following recommendations:[75,]

- For follicular lymphoma, marginal zone lymphomas, and mantle cell lymphoma, recommend allogeneic HCT as second-line consolidation therapy in select cases, which include mobilization failures and persistent bone marrow involvement. NCCN does note that with recent approval of CART T-cell therapy for relapsed/refractory MCL, allogeneic HCT has been deferred to disease relapse following multiple prior therapies in many NCCN member institutions.
- For DLBCL, "[a]llogeneic HCT should be considered in selected patients with mobilization failures and persistent bone marrow involvement or lack of adequate response to second-line therapy, though patients should be in CR or near CR at the time of transplant."
- For Burkitt lymphoma, allogeneic HCT is an option for selected patients who achieve a complete or partial response to second-line therapy.

National Comprehensive Cancer Network guidelines on T-cell lymphomas (v.1.2023) include the following recommendations:[1,]

"Second-line systemic therapy followed by consolidation with HDT [high-dose therapy]/ASCR [autologous stem cell rescue] or allogeneic HCT for those with a CR [complete response] or PR [partial response] is recommended for patients who are candidates for transplant."
"Allogeneic HCT should be considered for patients with acute or lymphoma [ATLL] subtype, if donor is available."

"In patients with acute or lymphoma subtypes who achieve a response to second-therapy, allogeneic HSCT should be considered if a donor is available."

"In patients [with T-PLL] who achieve a CR or PR following initial therapy, consolidation with allogeneic HCT should be considered. Autologous HCT may be considered, if a donor is not available and if the patient is not physically fit enough to undergo allogeneic HCT."

For hepatosplenic T-Cell Lymphoma (HSTCL), the guidelines state: "Consolidation therapy with allogeneic HCT is recommended for eligible patients with complete response or partial response after initial induction therapy or second-line therapy. Consolidation therapy with autologous HCT can be considered if a suitable donor is not available or for patients who are ineligible for allogeneic HCT." Furthermore, the guidelines state that: "Long-term remission is primarily or exclusively seen in those who have undergone consolidative HCT."

Of note, the NCCN does acknowledge the following: "Few studies have reported improved survival outcomes with autologous or allogeneic HCT as consolidation therapy for patients with disease in first or second remission. Some studies have also reported that graft-versus-lymphoma effect associated with allogeneic HCT may result in long-term survival in a significant proportion of patients with HSTCL and active disease at the time of transplant was not necessarily associated with poor outcomes." Nonetheless, they also state: "The goal of initial therapy is to induce complete or near complete response to allow successful bridging to HCT, preferably an allogeneic HCT."

The American Society of Transplantation and Cellular Therapy

In 2021, the American Society of Transplantation and Cellular Therapy (ASTCT), Center of International Blood and Marrow Transplant Research (CIBMTR), and the European Society for Blood and Marrow Transplantation (EBMT) formulated consensus recommendations regarding autologous HCT, allogeneic HCT, and chimeric antigen receptor (CAR) T-cell therapy for patients with MCL.[76,] The panel of experts, consisting of physicians and investigators, recommended the use of autologous HCT as consolidation therapy in newly diagnosed MCL patients (without TP53 mutation or bi-allelic deletion) who are in complete or partial remission after first-line therapies.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

Medicare has the following national coverage determination for the use of autologous cell transplantation for Hodgkin and non-Hodgkin lymphomas.[77,]
"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:

- Acute leukemia in remission who have a high probability of relapse and who have no human leukocyte antigens (HLA)-matched;
- Resistant non-Hodgkin's lymphomas or those presenting with poor prognostic features following an initial response;
- Recurrent or refractory neuroblastoma; or,
- 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%."

Ongoing and Unpublished Clinical Trials

Some currently unpublished phase 3 trials that might influence this review are listed in National Cancer Institute's Physician Data Query database.

Other currently unpublished trials that might influence this review are listed in Table 5.

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01811368	Use of Zevalin to Enhance the Efficacy of Non-Myeloablative Allogeneic Transplantation in Patients With Relapsed or Refractory CD20+ Non-Hodgkin's Lymphoma	20	Dec 2023
NCT01908777	A Phase 2 Multicenter Study of High Dose Chemotherapy With Autologous Stem Cell Transplant Followed by Maintenance Therapy With Romidepsin for the Treatment of TCell Non-Hodgkin Lymphoma	47	Jul 2023
NCT02859402	Allogenic Stem Cell Transplantation With 3-days Busulfan Plus Fludarabine as Conditioning in Patients With Relapsed or Refractory T-, NK/T-cell Lymphomas	34	Dec 2027
NCT03583424	A Phase I/II Trial of Venetoclax and BEAM Conditioning Followed by Autologous Stem Cell Transplantation for Patients With Primary Refractory Non-Hodgkin Lymphoma	19	Dec 2022
NCT00882895	Tandem Stem Cell Transplantation for Non-Hodgkin's Lymphoma	18	Jun 2028
Unpublished			
NCT01296256	Bendamustine, Cytarabine, Etoposide and Melphalan as Conditioning for Autologous Stem Cell Transplant in Patients With Aggressive Non-Hodgkin's Lymphoma	60	Nov 2015 (updated Feb 2016)

NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation:

- Referring physician history and physical
- Bone marrow transplant consultation report and/or progress notes documenting:
  - Diagnosis (including disease staging) and prognosis
  - Synopsis of alternative treatments performed and results
  - Specific transplant type being requested
- Surgical consultation report and/or progress notes
- Results of completed transplant evaluation including:
  - Clinical history including comorbidities
  - Specific issues identified during the transplant evaluation
  - Consultation reports/letters (when applicable)
  - Correspondence from referring physicians (when applicable)
  - Identification of donor for allogeneic related bone marrow/stem cell transplant (when information available)
- Medical social service/social worker and/or psychiatric (if issues are noted) evaluations including psychosocial assessment or impression of patient's ability to be an adequate candidate for transplant
- Radiology reports including:
  - Chest x-ray (CXR)
  - PET scan, CT scan, and bone survey (as appropriate)
- Cardiology procedures and pulmonary function reports:
  - EKG
  - Echocardiogram
  - Pulmonary function tests (PFTs)

- Biopsy/Pathology reports including:
  - Bone marrow biopsy
  - Lymph node biopsy (as appropriate)
- Laboratory reports

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	38204	Management of recipient hematopoietic progenitor cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
	38206	Blood-derived hematopoietic progenitor cell harvesting for transplantatio per collection; autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
	38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
	38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
	38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
	38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
	38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
	38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
	38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
	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
	S2140	Cord blood harvesting for transplantation, allogeneic
	S2142	Cord blood-derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related

Type	Code	Description
		complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre and post-transplant care in the global definition

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
01/07/2011	BCBSA Medical Policy adoption
04/01/2011	Policy revision with position change
05/29/2015	Policy title change from Hematopoietic Stem-Cell Transplantation for Non-Hodgkin Lymphoma Policy revision without position change
06/01/2017	Policy revision without position change
11/01/2017	Policy title change from Hematopoietic Stem Cell Transplantation for Non-Hodgkin Lymphomas Policy revision without position change
01/01/2018	Coding update
03/01/2018	Policy revision without position change
04/01/2019	Policy revision without position change
04/01/2020	Annual review. Policy statement, guidelines and literature updated. Coding update.
03/01/2021	Annual review. No change to policy statement. Literature review updated.
04/01/2022	Annual review. No change to policy statement. Literature review updated.
10/01/2022	Administrative update.
04/01/2023	Annual review. Policy statement, guidelines and literature updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will

be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas 8.01.20 **Policy Statement:** I. For patients with non-Hodgkin lymphoma (NHL) B-cell subtypes considered aggressive (except mantle cell lymphoma), either allogeneic hematopoietic cell transplantation (HCT) using a myeloablative conditioning regimen or autologous HCT may be considered **medically necessary** for **any** of the following reasons: A. 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 B. To achieve or consolidate a CR for those in a chemosensitive first or subsequent relapse C. To consolidate a first CR in patients with diffuse large B-cell lymphoma, with an age-adjusted International Prognostic Index score that predicts a high- or high-intermediate risk of relapse For patients with mantle cell lymphoma: II. Autologous HCT may be considered **medically necessary** to consolidate a first remission III. Allogeneic HCT, with myeloablative or reduced-intensity conditioning, may be considered **medically necessary** as salvage therapy IV. Autologous HCT is considered **investigational** as salvage therapy V. Allogeneic HCT is considered **investigational** to consolidate a first remission VI. For patients with NHL B-cell subtypes considered indolent, either allogeneic HCT using a myeloablative conditioning regimen or autologous HCT may be considered **medically necessary either** of the following reasons:	**Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas 8.01.20** **Policy Statement:** I. For individuals with non-Hodgkin lymphoma (NHL) B-cell subtypes considered aggressive (except mantle cell lymphoma), either allogeneic hematopoietic cell transplantation (HCT) using a myeloablative conditioning regimen or autologous HCT may be considered **medically necessary** for **any** of the following reasons: A. As salvage therapy for individuals who do not achieve a complete remission (CR) after first-line treatment (induction) with a full course of standard-dose chemotherapy B. To achieve or consolidate a CR for those in a chemosensitive first or subsequent relapse C. To consolidate a first CR in individuals 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 individuals with mantle cell lymphoma: II. Autologous HCT may be considered **medically necessary** to consolidate a first remission III. Allogeneic HCT, with myeloablative or reduced-intensity conditioning, may be considered **medically necessary** as salvage therapy IV. Autologous HCT is considered **investigational** as salvage therapy V. Allogeneic HCT is considered **investigational** to consolidate a first remission VI. For individuals with NHL B-cell subtypes considered indolent, either allogeneic HCT using a myeloablative conditioning regimen or autologous HCT may be considered **medically necessary either** of the following reasons:

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
A. As salvage therapy for patients who do not achieve CR after first-line treatment (induction) with a full course of standard-dose chemotherapy B. To achieve or consolidate CR for those in a first or subsequent chemosensitive relapse, whether or not their lymphoma has transformed to a higher grade	A. As salvage therapy for individuals who do not achieve CR after first-line treatment (induction) with a full course of standard-dose chemotherapy B. To achieve or consolidate CR for those in a first or subsequent chemosensitive relapse, whether or not their lymphoma has transformed to a higher grade
VII. Either autologous HCT or allogeneic HCT is considered **investigational** for **any** of the following: A. As initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for any NHL B. 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 C. To consolidate a first CR for those with indolent NHL B-cell subtypes	VII. Either autologous HCT or allogeneic HCT is considered **investigational** for **any** of the following: A. As initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for any NHL B. To consolidate a first CR for individuals with diffuse large B-cell lymphoma and an International Prognostic Index score that predicts a low- or low-intermediate risk of relapse C. To consolidate a first CR for those with indolent NHL B-cell subtypes
For patients with mature T-cell or natural killer cell (peripheral T-cell) neoplasms: VIII. Autologous HCT may be considered **medically necessary** to consolidate a first complete remission in high-risk subtypes (see Policy Guidelines section) IX. Autologous or allogeneic HCT (with myeloablative or reduced-intensity conditioning) may be considered **medically necessary** as salvage therapy X. Allogeneic HCT is considered **investigational** to consolidate a first remission	For individuals with mature T-cell or natural killer cell (peripheral T-cell) neoplasms: VIII. Autologous HCT may be considered **medically necessary** to consolidate a first complete remission in high-risk subtypes (see Policy Guidelines section) IX. Autologous or allogeneic HCT (with myeloablative or reduced-intensity conditioning) may be considered **medically necessary** as salvage therapy X. Allogeneic HCT is considered **investigational** to consolidate a first remission
	For individuals with hepatosplenic T-cell lymphoma: XIV. Allogenic HCT may be considered **medically necessary** to consolidate a first CR or partial response. XV. Autologous HCT may be considered **medically necessary** to consolidate a first response if a suitable donor is not available or for individuals who are ineligible for allogeneic HCT.

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
	XVI. Autologous or allogeneic HCT as initial therapy (i.e., without a full course of standard-dose induction chemotherapy) is considered **investigational**.
XI. Reduced-intensity conditioning with allogeneic HCT may be considered **medically necessary** as a treatment of NHL in patients who meet criteria for an allogeneic HCT but who do not qualify for a myeloablative allogeneic HCT (see Policy Guidelines section).	XI. Reduced-intensity conditioning with allogeneic HCT may be considered **medically necessary** as a treatment of NHL in individuals who meet criteria for an allogeneic HCT but who do not qualify for a myeloablative allogeneic HCT (see Policy Guidelines section).
XII. Tandem transplants are considered **investigational** to treat patients with any stage, grade, or subtype of NHL.	XII. Tandem transplants are considered **investigational** to treat individuals with any stage, grade, or subtype of NHL.
Note: Small lymphocytic lymphoma (SLL) may be considered a node-based variant of chronic lymphocytic leukemia (CLL). Therefore, small lymphocytic lymphoma is considered along with chronic lymphocytic leukemia in Blue Shield of California Medical Policy: Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia is considered in Blue Shield of California Medical Policy: Hematopoietic Cell Transplantation for Waldenström Macroglobulinemia	**Note**: Small lymphocytic lymphoma (SLL) may be considered a node-based variant of chronic lymphocytic leukemia (CLL). Therefore, small lymphocytic lymphoma is considered along with chronic lymphocytic leukemia in Blue Shield of California Medical Policy: Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia is considered in Blue Shield of California Medical Policy: Hematopoietic Cell Transplantation for Waldenström Macroglobulinemia.