Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

***Current Policy Effective Date: 11/1/24**
(See policy history boxes for previous effective dates)

Title: BMT - Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Description/Background

Treatment for Non-Hodgkin Lymphoma
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]). 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 or rejection or graft-versus-host disease.

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 recipient is a critical factor for achieving a successful outcome. Compatibility is established by typing human leukocyte antigens (HLAs) 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 six. An acceptable donor will match the recipient at all or most of the HLA loci.

Myeloablative (Conventional) Conditioning
The myeloablative (conventional) practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation. Intense conditioning regimens are limited to individuals whose health status is sufficient to tolerate the administration of cytotoxic agents with 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 initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self-immunologic effector cells. While the slower GVM effect is

considered the potentially curative component, it may be overwhelmed by substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host-disease, which increases susceptibility to opportunistic infections.

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

Reduced-Intensity or Non-myeloablative Conditioning for Allo-HCT
Reduced-intensity conditioning (RIC), sometimes referred to as non-myeloablative (NMA) conditioning, refers to the pretransplant use of lower doses of cytotoxic drugs with or without less intense regimens of radiotherapy than are used in myeloablative conditioning treatments. Although the definition of RIC/NMA 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/NMA is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. These RIC/NMA regimens range from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and individual condition. Individuals who undergo RIC/NMA 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.

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, title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

Medical Policy Statement

The safety and effectiveness of hematopoietic cell transplantation for non-Hodgkin lymphomas has been established. It may be considered a useful therapeutic option for individuals meeting specific criteria.

Inclusionary and Exclusionary Guidelines

Key: HCT= Hematopoietic Cell Transplant; CR=Complete remission.

For individuals with non-Hodgkin lymphoma (NHL) B-cell subtypes considered aggressive (except mantle cell lymphoma) or mature T-cell or NK-cell (peripheral T-cell) neoplasms

Inclusions:

Either allogeneic hematopoietic cell transplantation (HCT) using a myeloablative conditioning regimen or *autologous* HCT may be considered established when one of the following are met:

- 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;
- To achieve or consolidate a CR for those in a chemosensitive first or subsequent relapse;
- 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. IPI (International Prognostic Index) score will not be a necessary requirement for primary CNS diffuse large B-cell lymphoma since Primary CNS Lymphoma is a highly aggressive disease associated with poor prognosis.
- To consolidate a first CR in individuals with high risk subtypes of mature T-cell or NK-cell (peripheral T-cell) neoplasms..

Exclusions:

Individuals not meeting the above guidelines.

Mantle cell lymphoma:

Inclusions:

- *Autologous* HCT to consolidate a first remission;
- *Allogeneic* HCT, myeloablative or reduced-intensity conditioning, when used as salvage therapy.

Exclusions:

- *Autologous* HCT when used as salvage therapy;
- *Allogeneic* HCT to consolidate a first remission.

For individuals with NHL B-cell subtypes considered indolent

Inclusions:

- Either *allogeneic* HCT using a myeloablative conditioning regimen or *autologous* HCT when one of the following are met:
  - As salvage therapy for individuals who do not achieve CR after first-line treatment (induction) with a full course of standard-dose chemotherapy;
  - To achieve or consolidate CR for those in a first or subsequent chemosensitive relapse, whether or not their lymphoma has undergone transformation to a higher grade.

Exclusions:

- Either *autologous* HCT or *allogeneic* HCT is considered experimental/investigational:
  - As initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for any NHL;
  - 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;
  - To consolidate a first CR for those with indolent NHL B-cell subtypes.

For individuals with hepatosplenic T-cell lymphoma

Inclusions:

- *Allogeneic* HCT to consolidate a first CR or partial response;
- *Autologous* to consolidate a first response if a suitable donor is not available for individuals who are ineligible for allogeneic HCT.

Exclusions:

- *Autologous* or *allogeneic* HCT as initial therapy before the completion of the full course of induction chemotherapy

Reduced intensity conditioning *allogeneic* HCT

Inclusions:

- Treatment of NHL in individuals who meet criteria for an *allogeneic* HCT but who do not qualify for a myeloablative *allogeneic* HCT.

Exclusions:

- Those not meeting the above inclusionary guideline.

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

Policy Guidelines

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

- Reduced-intensity conditioning (RIC) would be considered an option in individuals who meet criteria for an allogeneic hematopoietic cell transplant (HCT) but whose age (typically older than 55 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy) preclude use of a standard conditioning regimen.
- In individuals who qualify for a myeloablative allogeneic hematopoietic 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 individuals with good performance status and minimal comorbidities more than allogeneic HCT with RIC.
- A chemosensitive relapse is defined as relapsed non-Hodgkin lymphoma (NHL) that does not progress *during or immediately after* standard-dose induction chemotherapy (i.e., achieves stable disease or a partial response).
- Transformation describes a lymphoma whose histologic pattern has evolved to a higher-grade lymphoma. Transformed lymphomas typically evolve from a nodular pattern to a diffuse pattern.
- Tandem transplants usually are defined as the planned administration of 2 successive cycles of high-dose myeloablative chemotherapy, each followed by infusion of autologous hematopoietic cells, whether or not there is evidence of persistent disease following the first treatment cycle. Sometimes, the second cycle may use non-myeloablative immunosuppressive conditioning followed by infusion of allogeneic stem cells.
- The term *salvage therapy* describes therapy given to individuals with refractory or relapsed disease. For individuals with peripheral T-cell lymphoma, salvage therapy includes individuals 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 individuals with progressive disease with first-line induction chemotherapy (refractory disease) or in individuals who relapse after a complete or partial response after initial induction chemotherapy, or individuals 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.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

38204	38205	38206	38207	38208	38209
38210	38211	38212	38213	38214	38215
38230	38232	38240	38241	S2140	S2142
S2150					

Other codes (investigational, not medically necessary, etc.):

N/A

POTENTIAL CONTRAINDICATIONS FOR TRANSPLANT:

Note: Final patient eligibility for transplant is subject to the judgment and discretion of the requesting transplant center.

The selection process for approved tissue transplants is designed to obtain the best result for each patient. Therefore, relative contraindications to HCT may include, but are not limited to:

- Poor cardiac function: Ejection fraction should be greater than 45% with no overt symptoms of congestive heart failure.
- Poor pulmonary function: Pulmonary function tests must be greater than or equal to 50% of predicted value.
- Poor renal function: Renal creatinine clearance should be greater than 40 ml/min or creatinine must be less than or equal to 2mg/dl.
- Poor liver function: There should be no history of severe chronic liver disease
- Presence of HIV or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus (HTLV-1).

Clinical documentation supplied to the health plan must demonstrate ***that attending staff at the transplant center have considered all contraindications*** as part of their overall evaluation of potential organ transplant recipient ***and have decided to proceed.***

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 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. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

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 World Health Organization/REAL classification recognized three major categories of lymphoid malignancies based on morphology and cell lineage: B-cell neoplasms, T-cell/natural killer cell neoplasms, and Hodgkin lymphoma.

The most recent lymphoma classification is the 2022 WHO classification (see Table 1).(4)

Table 1. Updated World Health Organization Classification (2022)

Tumour-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
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)

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).

Stage	Involvement
I	Involvement of a single lymph node region (I) or of a single extra lymphatic 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 extra lymphatic 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 extra lymphatic organ or site (IIIE) or by involvement of the spleen (IIIS) or both (IIISE)
IV	Diffuse or disseminated involvement of one or more extra lymphatic organs or tissues with or without associated lymph node enlargement

INDOLENT B-CELL LYMPHOMAS

Clinical Context and Therapy Purpose

The purpose of autologous hematopoietic cell transplantation as first-line therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with indolent B-cell non-Hodgkin lymphomas.

The following PICOs were used to select literature to inform this review.

Populations

The relevant population of interest are individuals with indolent B-cell non-Hodgkin lymphomas.

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.

Interventions

The therapy being considered is autologous hematopoietic cell transplantation as first-line therapy or for relapsed or refractory disease.

Comparators

Comparators of interest include standard of care.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, 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 longer 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 Lymphoma

Systematic Reviews
Al Khabori et al (2012) performed a systematic review and meta-analysis of the use of autologous hematopoietic cell transplantation (HCT) in untreated, advanced follicular lymphoma (FL).(7) Four RCTs comparing autologous HCT to conventional chemotherapy (N=941) were included. Three trials reported overall survival (OS); moderate quality evidence from these trials did not show improvement in OS with the use of HCT as part of the initial treatment of FL. Adverse events including treatment-related mortality and the development of myelodysplastic syndrome, acute myeloid leukemia, and solid tumors, did not differ between treatment arms.

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.(8) Five RCTs involving 1093 individuals were included, with 4 trials in previously untreated individuals and 1 in relapsed individuals. 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 (HR: 0.42 (95% confidence interval [CI]: 0.33 to 0.54; p<0.001). However, there was no statistically significant OS advantage (HR: 0.97; 95% 0.76 to 1.24; p=0.81). In the four trials in previously untreated patients, there were no statistically significant differences between HCT and the control-arm in terms of treatment-related mortality (RR: 1.28; 95% CI: 0.25 to 6.61; p=0.77), secondary acute myeloid leukemia/myelodysplastic syndromes (RR: 2.87; 95% CI: 0.7 to 11.75; p=0.14) or solid cancers (RR: 1.20; 95% CI: 0.25 to 5.77; p=0.82). Adverse events were rarely reported and were more frequent in individuals 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 the results of a Phase 3, randomized, multicenter trial of patients with high-risk FL, treated at diagnosis.(9) A total of 134 patients were randomized to rituximab-supplemented high-dose chemotherapy plus autologous HCT or up to six courses of cyclophosphamide, doxorubicin (or 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 complete remission (CR) was 85% with HCT and 62% with CHOP-R. At a median follow-up of 51 months, the four-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.(10) A total of 209 patients received cyclophosphamide, doxorubicin, etoposide, prednisolone, interferon plus cyclophosphamide, doxorubicin, etoposide, prednisolone, and 131 patients received CHOP followed by high-dose chemotherapy with total body irradiation and autologous HCT. Response rates were similar in both groups (79% and 78% after induction therapy, respectively). After a median follow-up of 7.5 years, intention-to-treat analysis showed no difference between the arms for OS (p=0.53) or EFS (p=0.11).

Deconinck et al (2005) investigated the role of autologous HCT as initial therapy in 172 patients with FL considered at high-risk due to the presence of either B symptoms (i.e., weight loss, fever, or night sweats), a single lymph node larger than 7 cm, more than three involved nodal sites, massive splenomegaly, or a variety of other indicators of high tumor burden.(11) The patients were randomized to an immunochemotherapy regimen or 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.(12) Patients were randomized to receive either consolidative therapy with autologous HCT or interferon therapy. The 5-year PFS rate was considerably higher in the autologous HCT arm (64.7%) compared to the interferon arm (33.3%). However, the median follow-up of patients in this trial was too short to permit any comparison of OS.

HCT for Relapsed or Refractory, Indolent Non-Hodgkin Lymphomas

Randomized Controlled Trial

In the most patients with FL relapse, and with relapsed disease, cure is very unlikely, with a median survival of 4.5 years after recurrence.(13) In the European CUP trial (2004), 89 patients with relapsed, non-transformed FL with partial response (PR) or CR after standard induction chemotherapy were randomized to one of three arms: three 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).(12) OS rates at four years for the chemotherapy vs unpurged vs purged arms were 46%, 71%, and 77%, respectively. Two-year PFS rates were 26%, 58%, and 55%, respectively. No difference was found between the autologous HCT arms. Although several studies have consistently shown

improved disease-free survival with autologous HCT for relapsed FL, this study was the first to show a difference in OS benefit.

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.(14) All cases presented refractory or relapsed Hodgkin lymphoma (n=22) or a number of subtypes of NHL (n=18). Among the regimens given to patients were ifosfamide, carboplatin, and etoposide, and carmustine, etoposide, cytosine arabinoside, and melphalan; additionally, doxorubicin, bleomycin, vinblastine, and dacarbazine were administered to Hodgkin lymphoma patients, and R-CHOP was given to those with NHL. Given the small sample size, multivariate analysis was precluded; however, univariate analysis found no statistically significant differences between groups, except regarding chemosensitive vs chemoresistant cases and between patients undergoing ifosfamide, carboplatin, and etoposide and carmustine, etoposide, cytosine arabinoside and melphalan regimens. After salvage therapy, 22 patients showed a PR; six patients showed a CR, and eight had stable disease. The study found that the 5-year OS rate was significantly higher for chemosensitive patients (50%) than for chemoresistant patients (22%; p=0.02); however, given the small size of the population, other analyses were primarily descriptive or showed no statistical significance.

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 two years of frontline immunochemotherapy.(15) The analysis included patients with non-transformed FL treated with rituximab. ETF was defined as relapse or progression within two 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 two in PR2, but who did not experience ETF). No significant difference was found between the ETF and non-ETF groups in five-year PFS (49% vs. 60%, respectively; p= 0.49) or 5-year OS (81% vs. 83%, p= 0.8). 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, randomized trials, 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 hematopoietic cell transplantation as consolidation therapy after first complete remission is to provide a treatment option that is an alternative to or an

improvement on existing therapies in individuals with aggressive B-cell non-Hodgkin lymphomas, excluding mantle cell lymphoma.

The following PICOs were used to select literature to inform this review.

Populations
The relevant population of interest are individuals with aggressive B-cell non-Hodgkin lymphomas, excluding mantle cell lymphoma.

Aggressive NHL has a shorter natural history; however, 30% to 60% of these patients can be cured with intensive combination chemotherapy regimens.(1) Aggressive lymphomas include DLBCL, MCL, PTCL, anaplastic large-cell lymphoma, and Burkitt lymphoma.

Risk Assessment
Oncologists developed a clinical tool to aid in predicting the prognosis of patients with aggressive NHL (specifically DLBCL), referred to as the International Prognostic Index (IPI).(16) 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).(17)

Interventions
The therapy being considered is autologous hematopoietic cell transplantation as first line consolidation therapy after first complete remission or for relapsed disease.

Comparators
Comparators of interest include standard of care.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, 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 principles described in the first indication.

Review of Evidence

HCT for First-Line Therapy or Consolidation Therapy for Aggressive Non-Hodgkin Lymphomas

Systematic Reviews
Greb et al (2008) undertook 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=0.004). However, autologous HCT did not affect OS when compared with conventional chemotherapy. According to the IPI, subgroup analysis of prognostic groups showed no survival differences between autologous HCT and conventional chemotherapy in 12 trials, and EFS also did not differ between the two 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.(19-22) 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 eight-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=0.04) and disease-free survival (DFS; 55% vs. 39%, respectively; RR=1.56,

p=0.02) for patients at elevated risk of relapse who received autologous HCT as consolidation therapy.

A large, multigroup, prospective, randomized phase 3 comparison of these strategies, 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 (26-28) 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 the results of a phase III multicenter, randomized trial comparing sequential high-dose chemotherapy with autologous HCT to standard CHOP as first-line therapy in 129 patients with aggressive NHL.(29) Remission rates were similar in the two groups, and after a median observation time of 48 months, there was no difference in OS (46% in the sequential autologous HCT group vs 53% in the group that received CHOP (p=0.48). Sequential autologous HCT did not confer any survival benefit as initial therapy in patients with aggressive NHL.

Baldissera et al (2006) reported on the results of a prospective RCT comparing high-dose chemotherapy plus autologous HCT with conventional chemotherapy as first-line therapy in 56 patients with high-risk aggressive NHL.(30) The 5-year actuarial OS and PFS rates did not differ statistically between the two study groups; only DFS differed statistically (97% for the autologous HCT group vs 47% for the conventional group; p=0.02.)

Olivieri et al (2005) reported on a randomized study of 223 patients with aggressive NHL using upfront high-dose chemotherapy plus autologous HCT vs conventional chemotherapy plus autologous HCT in cases of failure.(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=0.5), DFS (62% and 71%, p=0.2), or PFS (44.9% and 40.9%, p=0.7, all respectively) between the 2 groups. Patients with aggressive NHL did not benefit from upfront autologous HCT.

Results of a phase 3 multicenter randomized trial (SWOG-9704) of autologous HCT as consolidation for aggressive (high-intermediate or high-risk) diffuse B-cell NHL were published in 2013.(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 end points 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=0.005). The 2-year OS rates in the HCT and control group were 74% and 71%, respectively (HR=1.26; 95% CI, 0.82 to 1.94; p=0.30). Unplanned exploratory analyses showed a differential treatment effect by disease risk level. Among high-risk patients, the 2-year OS rate was 82% in the HCT group and 64% in the control group (p=0.01). The main results of this trial comport with earlier study results in not discerning a significant effect of early autologous HCT on OS among a group of patients with

high-, intermediate-, and high-risk diffuse B-cell NHL. However, the survival curve appeared to plateau among the high-risk HCT patients out to 10 years after study registration. Although this evidence was from exploratory subset analysis, it further supports the efficacy of this approach in such cases compared with nontransplant strategies.

A 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 two or three risk factors according to age-adjusted IPI. Neither group achieved the primary end point, which was CR greater than 50%, as defined by 2007 International Harmonization Project criteria, with 47% (95% CI, 38% to 67%) of doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone plus rituximab patients and 39% 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 two 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 Δ SUVmax (PFS for the respective groups was 80% vs 56%, $p<0.001$; OS was 87% vs 69% in patients with a Δ SUVmax <66%, $p=0.003$). When Δ SUVmax was assessed following PET4, similar improvements were observed: the 4-year PFS rate was 84% in those showing a Δ SUVmax greater than 70%, compared with 35% in those with a Δ SUVmax of 70% or less ($p<0.001$); likewise, OS rates were 91% and 57% for the respective groups ($p<0.001$). Differences between the potential treatments (standard chemotherapy, autologous HCT, or salvage therapy) were not statistically significant.

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 in 2017 of 20 individuals (13 men, 7 women) treated with autologous HCT for systemic NHL with some form of central nervous system (CNS) involvement.(35) Most patients presented with DLBCL histology (n=17 [85%]), and CNS involvement varied: the help 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. PFS 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 one year (95%; 95% CI, 68% to 99%) and four 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.

HCT 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 Chemotherpay 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=0.001); the OS rate was 53% in the transplant group and 32% in the nontransplant group (p=0.038).

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, auto-HCT had a significantly higher survival rate than allo-HCT

(55% [95% CI: 36% to 70%] vs. 32% [95% CI: 18% to 46%]; *p*= 0.036). 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 auto-HCT (23% [95% CI: 12% to 35%] vs. 3.2% [95% CI: 2.4% to 14%]; *p*= 0.017). For relapse, no statistically significant difference was found between allo-HCT and auto-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 complete remission, the evidence includes randomized trials 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 complete remission. 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 allogeneic hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with non-Hodgkin lymphomas, excluding mantle cell lymphoma.

The following PICOS were used to select literature to inform this review.

Populations
The relevant population of interest are individuals with non-Hodgkin lymphomas, excluding mantle cell lymphoma.

Interventions
The therapy being considered is tandem autologous and allogeneic hematopoietic cell transplantation.

Comparators
Comparators of interest include standard of care.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, 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 principles described in the first indication.

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 three.(39) After induction, responders underwent tandem autologous transplantation; 31 of 41 evaluable patients completed the program. There were four toxicity-related deaths. The primary end point of the trial was CR rate, which was 49%. With a median follow-up of 114 months for surviving patients, the OS rate was 51%, and 19 (86%) of the 22 patients who reached a CR were alive and relapse-free. Prospective evaluation of the quality of life and comorbidities of surviving patients did not reveal long-term toxicities.

A pilot study in 2005 evaluated 41 patients with poor-risk NHL and Hodgkin disease who were given tandem high-dose chemotherapy and autologous HCT.(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) allogeneic HCT (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 five 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 five-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 two-year treatment-related mortality incidence was 6%. These results suggested tandem autologous-allogeneic transplantation is feasible in high-risk NHL patients having a human leukocyte antigen–identical donor, but further study is necessary to establish its role in this setting.

Satwani et al (2015) conducted a nonrandomized 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).

Mantle Cell Lymphoma

Clinical Context and Therapy Purpose

The purpose of autologous, allogeneic, or tandem hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with mantle cell lymphoma.

The following PICOs were used to select literature to inform this review.

Populations

The relevant population of interest are individuals with 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.

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

Interventions

The therapy being considered is autologous, allogeneic, or tandem hematopoietic cell transplantation.

Comparators

Comparators of interest include standard of care.

MCL is rarely, if ever, cured with conventional therapy, and no standardized therapeutic approach to MCL is used.

Outcomes

The general outcomes of interest are overall survival, disease-specific survival, 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 principles described in the first indication.

Review of Evidence

Autologous HCT

Randomized Controlled Trials

To improve outcomes of MCL, several phase II 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 in these studies were likely due to different time points of transplant (first vs. second remission) and other 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=0.003). There was also a significant improvement in the 3-year PFS rate in the autologous HCT arm (54%) vs the interferon arm (25%; p=0.01). At the time of the reporting, no advantage was seen in OS, with 3-year OS rates of 83% and 77%, respectively. The results also suggested that the impact of autologous HCT could depend on the patient's remission status before the transplant, with a median PFS of 46 months in patients in CR and 33 months in patients in PR.

Zoellner et al (2021) conducted a post-hoc analysis of an open-label, multicenter, randomized phase 3 trial on previously untreated MCL patients.(46) A total of 269 patients were randomized to receive myeloablative radio-chemotherapy 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.

Observational studies
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).(47) The OS and PFS rates at three years among patients transplanted in CR or PR were 93% and 63% compared with 46% and 36%, all respectively, for patients transplanted with relapsed or refractory disease. The hazard of mortality among patients transplanted with relapsed or refractory disease was 6.1 times that of patients transplanted in first CR or PR (p<0.001).

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.(48) Investigators noted a significant improvement in PFS for patients who underwent transplantation during first CR, compared with patients with other disease statuses (i.e., PR, chemosensitive, chemorefractory): in univariate analysis, PFS for first CR patients was 48 months (95% CI, 37 to 62 months) compared with 26 months (95% CI, 66 to 128 months) for other statuses (p=0.01). There was a similar association between first CR status and OS, compared with other statuses: 97 months vs 57

months (p=0.03). When adjusted for multiple variables, both associations were also statistically significant (RR for PFS=1.6 [95% CI, 1.1 to 2.2], p=0.015 vs RR for OS=0.8 [95% CI, 1.2 to 2.7], p=0.003). During univariate analysis, prior exposure to rituximab was associated with a greater PFS and OS (respectively, p=0.02; p<0.001); however, this association was confirmed by multivariate analysis because of the limited data on rituximab in all patients. The investigators noted that improvements in survival rates were restricted to patients who received transplantation during first CR; for more uncertain statuses (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 post-transplantation, supporting the use of autologous HCT in patients with CR or near CR.

Metzner et al (2023) reported long-term outcomes for a series of 65 individuals with MCL who received autologous HCT.(49) 54 (83%) received first-line autologous HCT, 10 (15%) received second-line autologous HCT. 10-year OS and PFS after first-line HCT were 64% and 52%, respectively. 10-year OS and PFS after second-line HCT was 50% and 20%. Treatment-related mortality 3 months after HCT was 1.5%. At the time of publication, 26 of the individuals who received first-line HCT remained in complete remission up to 19 years following HCT.

Allo-HCT

Several studies have assessed allo-HCT in patients with MCL.(50) Khouri et al (2003) reported on results of allo-HCT with RIC in 18 patients with relapsed MCL; after a median follow-up of 26 months, the actuarial probability of EFS was 82% at three years.(51) Maris et al evaluated allogeneic HCT in 33 patients with relapsed and recurrent MCL. At 2 years, the relapse and non-relapse mortality rates were 9% and 24%, respectively, and the OS and DFS were 65% and 60%, respectively.(52) Kruger 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. (53) 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 HCT and Allo-HCT

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

Tam et al (2009) reported a retrospective study which included all patients with MCL who had undergone HCT in sequential phase II protocols (autologous or nonmyeloablative allogeneic) at the University of Texas M.D. Anderson Cancer Center between February 1990 and June 2007.(54) 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 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=0.01 and 0.02 vs AUTO1), and the median PFS and OS durations were 27 and 52 months, respectively. These inferior results for both PFS and OS compared with AUTO1 patients were confirmed in a multivariate analysis that accounted for differences in baseline factors.

Of the patients who underwent nonmyeloablative allo-HCT for relapsed or refractory MCL, 20% did not respond to initial chemotherapy but experienced a PR or better to salvage therapy with R-hyper-CVAD. Thirty-one percent were in the second remission, 31% were in third or subsequent remission, and 17% had a refractory relapse and received a transplant in less than PR. With a median follow-up of 56 months (range, 19-110 months), the median PFS duration was 60 months, and the median OS had not yet been reached. The 6-year 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=0.01 for PFS; p=0.005 for OS [4-year landmark for OS]). Compared with AUTO1 patients, the patients who received allo-HCT with RIC had an initially lower OS; however, this reversed at 8 years among nonmyeloablative allogeneic patients.

The 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 five years and nine years; whereas patients who received an autologous transplant had a median remission of 2 years and experienced a continuous pattern of relapse.

Therefore, nonmyeloablative allo-HCT might be salvaging treatment option for patients no longer curable with maximum cytotoxic strategies.

As noted in the Tam et al study,(54) 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.(44,55) 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.(55)

Section Summary: 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.

Peripheral T-Cell Lymphoma (Mature T-Cell or Natural Killer Cell Neoplasms)

Clinical Context and Therapy Purpose
The purpose of autologous or allogeneic hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with peripheral T-cell lymphoma (PTCL).

The following PICOs were used to select literature to inform this review.

Populations
The relevant population of interest are individuals with peripheral T-cell lymphoma (PTCL).

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.

Interventions
The therapy being considered is autologous or allogeneic hematopoietic cell transplantation.

Comparators
Comparators of interest include standard of care.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, 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 principles described above.

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.(56) 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 Trials
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.(57) 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 and Single-Arm 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 the large prospective study of 83 patients with PTCL from multiple centers to undergo autologous HCT as first-line therapy.(58) 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 the results of 2 phase II studies involving 62 patients with advanced stage PTCL at diagnosis.(59) In an intention-to-treat analysis, 46 (74%) of the 62 completed the whole program. Sixteen patients failed to undergo transplant due to early

disease progression and/or toxicity. Pretransplant, 56% of patients were in CR and 16% in PR. Median follow-up was 76 months, with estimated 12-year OS, DFS, and EFS rates of 34%, 55%, and 30%, respectively. Five-year EFS and OS rates were 40% and 50%, respectively. Multivariate analysis revealed that patients who achieved CR before HCT had a statistically significant benefit in OS and EFS ($p<0.001$).

Mercadal et al (2008) reported results of a Phase 2 trial involving 41 patients consecutively diagnosed with PTCL (median age: 47 years).(60) Patients who responded to induction chemotherapy (CR or PR) went on to autologous HCT. Twenty-four patients responded (CR n=20, PR n=4). Seventeen of these 24 underwent HCT (the remaining patients did not, for various reasons including lack of stem cell mobilization, toxicity, and early relapse). For patients who completed the entire procedure, CR was 51% and PR, 7%. Median follow-up was 3.2 years (range, 0.6-8.1 years), and 5 of 21 CR patients relapsed, and 2 died in CR due to a secondary malignancy. The 4-year PFS rate was 30% (95% CI, 15% to 45%), and the OS rate was 39% (95% CI, 22% to 56%). No difference in OS was noted among the 24 patients eligible for transplant, 17 of whom did, and 7 of whom did not undergo a transplant.

A prospective phase 2 trial by Rodriguez et al (2007) showed that autologous HCT as first-line consolidation therapy improved treatment outcome in patients responding to induction therapy.(61) Nineteen of 26 patients who showed CR or PR to induction therapy received an autologous HCT. At 2 years' posttransplant, OS, PFS, and DFS were 84%, 56%, and 63%, respectively.

Wang et al (2018) conducted a retrospective study to investigate the efficacy of HCT in treating extra nodal 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. Analysis found that 5-year overall survival was 79.3% for the HCT group compared with 52.3% for the control group (p=0.026). Limitations included the retrospective design, lack of multiple centers, and a small sample size.(62)

Wu et al (2023) reported outcomes of a retrospective study including a consecutive series of individuals with PTCL who received consolidative autologous HCT after first-line therapy (n=120) from 14 transplant centers in China between 2001 and 2019.(63) A comparator group of consecutive individuals with PTCL who did not receive autologous HCT (n=317) and were treated over the same time frame were also selected for inclusion. The individuals in the no-HCT group primarily did not receive HCT due to contraindications, failure to achieve disease remission, or economic reasons. Survival with and without HCT was compared using propensity score matching for pathological subtype, IPI score, and remission status. The median follow-up time was 40 and 68 months in the HCT and no-HCT groups. 3-year OS was 82% vs 68% (p=.001) for the HCT vs non-HCT groups in the propensity-score matched analysis.

First-Line Allo-HCT for Peripheral T-Cell Lymphoma

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.(64) 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.(65) 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

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

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

Song et al (2003) compared the outcomes of 36 patients with PTCL who underwent autologous HCT with 97 patients with relapsed DLBCL.(66) 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=0.41 and 0.29, respectively). The patients with unspecified PTCL had an inferior EFS rate when compared with the DLBCL patients (23%, p=0.028), and those with ALCL had a nonsignificant trend for improved EFS (67%, p=0.41).

Rodriguez et al (2007) reported the largest series of patients with refractory or relapsed PTCL who received an autologous HCT.(67) 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 Allo-HCT (Relapsed or Refractory) for 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.(58)

Kyriakou et al (2009) reported 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.(68) 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. Non-relapse 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: 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; randomized trials 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 chemotherapy 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.

Hepatosplenic T-cell Lymphoma

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 individuals 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 (Hepatosplenic T-cell Lymphoma) HSTCL after first response (complete or partial) to induction chemotherapy.

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.

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.

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 principles described above.

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.(69) 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).(70) 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)	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)	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)					
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)					
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.(71) 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.(72) 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: 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.

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

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

For individuals who have NHL, excluding MCL, who receive tandem autologous HCT and allo-HCT, the evidence includes several nonrandomized trials. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. No randomized studies have been conducted on the use of tandem HCT for the treatment of NHL, and the published evidence comprises of a limited number of patients. Presently, conclusions on the use of tandem transplants cannot be made

about autologous and allo-HCT. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have mantle cell lymphoma who receive autologous, allogeneic, or tandem HCT, the evidence includes case series and RCTs. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have PTCL who receive autologous HCT or allo-HCT, the evidence mainly includes prospective trials and case reports/series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. The role of HCT in PTCL is not well-defined. Few studies have been conducted, and most were performed retrospectively, with a limited number of patients; moreover, the patient populations were heterogeneous and included good- and poor-risk patients in the same study. Patient population and characteristics of the studies can be explained partially by the rarity and heterogeneity of the particular group of lymphomas addressed. Additionally, studies of this nature often mix 3 types of patients: 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; randomized trials 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 chemotherapy plus consolidation with autologous HCT as the first-line therapy for adults with nodal PTCL demonstrated improved OS and progression-free (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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have hepatosplenic T-cell lymphoma (HSTCL) who receive autologous or allo-HCT as consolidation therapy after first response (complete or partial), the evidence includes observational studies and systematic reviews. Relevant outcomes are OS, DSS, change in disease status, morbid events, and treatment-related mortality and morbidity. 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. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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			
NCT01827605	A Phase III Multicenter, Randomized Study Comparing Consolidation With 90yttrium-Labeled Ibritumomab Tiuxetan (Zevalin®) Radioimmunotherapy Vs Autologous Stem Cell Transplantation (ASCT) in Patients With Relapsed/Refractory Follicular Lymphoma (FL) Aged 18-65 Years	159	Jan 2024
NCT02881086	Treatment Optimization in Adult Patients With Newly Diagnosed Acute Lymphoblastic Leukemia (ALL) or Lymphoblastic Lymphoma by Individualised, Targeted and Intensified Treatment - a Phase IV-trial With a Phase III-part to Evaluate Safety and Efficacy of Nelarabine in T-ALL Patients	1000	Jul 2025
NCT00882895	Tandem Stem Cell Transplantation for Non-Hodgkin's Lymphoma	18	Jun 2028
NCT03267433	A Randomized Phase III Trial of Consolidation With Autologous Hematopoietic Cell Transplantation Followed by Maintenance Rituximab vs. Maintenance Rituximab Alone for Patients With Mantle Cell Lymphoma in Minimal Residual Disease-Negative First Complete Remission	689	Jan 2032

NCT: national clinical trial.

Supplemental Information

CLINICAL INPUT RECEIVED THROUGH PHYSICIAN SPECIALTY SOCIETY AND ACADEMIC MEDICAL CENTER

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 for February 2011. 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. Reviewer input was solicited particularly for the use of HCT in MCL and PTCL. There was uniform agreement for the use of autologous HCT to consolidate a first remission in MCL. There was 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 PTCL, there was general agreement on the use of autologous HCT to consolidate a CR in high-risk patients and in the salvage setting. Input was split on the use of allogeneic HCT to consolidate a first CR or as salvage therapy, but there was more support to consider it medically necessary in both settings.

2009 Input

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

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network Guidelines

Current National Comprehensive Cancer Network guidelines on B-cell lymphomas include the following recommendations:(73)

- 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]llogenic 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 include the following recommendations:(74)

For peripheral T-cell lymphoma: “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.”

For adult T-cell leukemia/lymphoma:

- “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.”

For T-cell Prolymphocytic Leukemia: “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):

- "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."
- "Long-term remission is primarily or exclusively seen in those who have undergone consolidative HCT."
- “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.
- “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.(75) 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.

The ASTCT Committee on Practice Guidelines published guidance on transplantation and cellular therapies in Diffuse Large B Cell Lymphoma (DLBCL) in 2023.(76) The committee made the following recommendations:

- "The panel does not recommend autologous HCT in DLBCL (regardless of IPI score) as consolidation in complete remission after first-line (R-CHOP or similar) therapy." Grading: A
- "Autologous HCT may be considered for eligible patients with DLBCL with secondary CNS involvement at diagnosis achieving complete remission and with undetectable CNS disease after first-line therapy." Grading: C
- "The panel recommends consolidation with autologous HCT for eligible primary CNS lymphoma patients in CR1." Grading: A
- "In DLBCL patients with early relapse who achieve a complete remission with salvage therapy, the panel considers autologous HCT an acceptable consolidation therapy in eligible patients." Grading: B
- "In DLBCL patients with early relapse who achieve a partial remission with salvage therapy, the panel considers autologous HCT an acceptable consolidation therapy in eligible patients." Grading: B

- "In DLBCL patients with late relapse, the panel recommends autologous HCT consolidation therapy in eligible patients who have achieved a complete or partial remission after second-line therapies." Grading: A
- "The panel recommends allogeneic HCT in eligible DLBCL patients relapsing/progressing after CAR-T therapy if they achieve a complete or partial remission with subsequent antilymphoma therapies." Grading: C
- "The panel recommends allogeneic HCT in eligible relapsed or refractory DLBCL patients after autologous HCT failure in regions without access to CAR-T therapy, and in those with CAR T cell manufacturing failure, ideally after achieving a complete or partial remission with subsequent antilymphoma therapies." Grading: C

Grading of recommendations: A, There is good research-based evidence to support the recommendation; B, There is fair research-based evidence to support the recommendation; C, The recommendation is based on expert opinion and panel consensus; X, There is evidence of harm from this intervention.

Government Regulations
National:

There are numerous autoimmune diseases and the Centers for Medicare and Medicaid Services have not issued a national coverage determination (NCD) for stem cell transplantation for each disease. CMS has a general NCD for stem cell transplantation.

Medicare National Coverage Determinations Manual 100-3, Chapter 1, Part 2, Section 110.23, "Stem Cell Transplantation." Effective date:3/6/24; Implementation Date: 10/7/24

A. General

Stem cell transplantation is a process in which stem cells are harvested from either a patient's (autologous) or donor's (allogeneic) bone marrow or peripheral blood for intravenous infusion. Autologous stem cell transplantation (AuSCT) is a technique for restoring stem cells using the patient's own previously stored cells. AuSCT must be used to effect hematopoietic reconstitution following severely myelotoxic doses of chemotherapy (HDCT) and/or radiotherapy used to treat various malignancies. Allogeneic hematopoietic stem cell transplantation (HSCT) is a procedure in which a portion of a healthy donor's stem cell or bone marrow is obtained and prepared for intravenous infusion. Allogeneic HSCT may be used to restore function in recipients having an inherited or acquired deficiency or defect. Hematopoietic stem cells are multi-potent stem cells that give rise to all the blood cell types; these stem cells form blood and immune cells. A hematopoietic stem cell is a cell isolated from blood or bone marrow that can renew itself, differentiate to a variety of specialized cells, can mobilize out of the bone marrow into circulating blood, and can undergo programmed cell death, called apoptosis - a process by which cells that are unneeded or detrimental will self-destruct.

The Centers for Medicare & Medicaid Services (CMS) is clarifying that bone marrow and peripheral blood stem cell transplantation is a process which includes mobilization, harvesting, and transplant of bone marrow or peripheral blood stem cells and the administration of high dose chemotherapy or radiotherapy prior to the actual transplant. When bone marrow or peripheral blood stem cell transplantation is covered, all necessary steps are included in

coverage. When bone marrow or peripheral blood stem cell transplantation is non-covered, none of the steps are covered.

- **Allogeneic Stem Cell Transplantation**
  - No indications found for Non-Hodgkin Lymphomas

- **Autologous STEM CELL Transplantation (AuSCT)**
  - Effective for services performed on or after April 28, 1989, AuSCT is considered reasonable and necessary under §l862(a)(1)(A) of the Act for the following conditions and is covered under Medicare for patients with:
    - Resistant non-Hodgkin's lymphomas or those presenting with poor prognostic features following an initial response

See determination for complete information.

(This NCD last reviewed March 2024.)

Local:

There is no local coverage determination on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- BMT – Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia
- BMT – Hematopoietic Cell Transplantation for Acute Myeloid Leukemia
- BMT – Hematopoietic Cell Transplantation for Autoimmune Diseases
- BMT – Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Cell Lymphocytic Lymphoma – Autologous or Allogeneic
- BMT – Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia
- BMT – Hematopoietic Cell Transplantation for CNS Tumors, Embryonal Tumors and Ependymoma
- BMT – Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer
- BMT – Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias (Allogeneic)
- BMT – Hematopoietic Cell Transplantation for Germ-Cell Tumors
- BMT – Hematopoietic Cell Transplantation for Hodgkin Lymphoma
- BMT – Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
- BMT – Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms
- BMT – Hematopoietic Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome
- BMT – Hematopoietic Cell Transplantation for Primary Amyloidosis
- BMT – Hematopoietic Cell Transplantation for Solid Tumors of Childhood
- BMT – Hematopoietic Cell Transplantation for Waldenström’s Macroglobulinemia
- BMT – Malignant Astrocytomas and Gliomas (Autologous)

- Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant
- Orthopedic Applications of Stem-Cell Therapy (Including Allografts and Bone Substitutes used with Autologous Bone Marrow)

References

1. National Cancer Institute. Adult Non-Hodgkin Lymphoma Treatment (PDQ®)–Health Professional Version. 2021; https://www.cancer.gov/types/lymphoma/hp/adult-nhl-treatment-pdq. Accessed November 15, 2023.
2. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood. Sep 1 1994;84(5):1361-1392. PMID 8068936.
3. Harris NL, Jaffe ES, Diebold J et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the clinical advisory committee meeting-Arlie House, Virginia, 1997. J Clin Oncol 1999; 17(12):3835. PMID 10643532
4. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. Jul 2022; 36(7): 1720-1748. PMID 35732829
5. American Cancer Society. Non-Hodgkin Lymphoma (Adults). https://www.cancer.org/cancer/non-hodgkin-lymphoma/about.html. Accessed November 16, 2023.
6. Laport GG. The role of hematopoietic cell transplantation for follicular non-Hodgkin's lymphoma. Biol Blood Marrow Transplant 2006; 12(1 suppl 1):59-65. PMID 16399587
7. Al Khabori M, de Almeida JR, Guyatt GH et al. Autologous stem cell transplantation in follicular lymphoma: a systematic review and meta-analysis. J Natl Cancer Inst 2012; 104(1):18-28. PMID 22190633
8. Schaaf M, Reiser M, Borchmann P et al. High-dose therapy with autologous stem cell transplantation versus chemotherapy or immuno-chemotherapy for follicular lymphoma in adults. Cochrane Database Syst Rev 2012; 1:CD007678. PMID 22258971
9. Ladetto M, De Marco F, Benedetti F et al. for Gruppo Italiano Trapianto di Midollo Osseo (GITMO): Intergruppo Italiano Linfomi (IIL). Prospective, multicenter randomized GITMO/IIL trial comparing intensive R-HDS) versus conventional (CHOP-R) chemoimmunotherapy in high-risk follicular lymphoma at diagnosis: the superior disease control of R-HDS does not translate into an overall survival advantage. Blood 2008; 111(8):4004-13. PMID 18239086
10. Sebban C, Mounier N, Brousse N et al. Standard chemotherapy with interferon compared with CHOP followed by high-dose therapy with autologous stem cell transplantation in untreated patients with advanced follicular lymphoma: the GELF-94 randomized study from the Groupe d'Etude des Lymphomes de l'Adulte (GELA). Blood 2006; 108(8):2540-4. PMID 16835383
11. Deconinck E, Foussard C, Milpied N et al. High-dose therapy followed by autologous purged stem cell transplantation and doxorubicin based chemotherapy in patients with advanced follicular lymphoma: a randomized multicenter study by GOELAMS. Blood 2005; 105(10):3817-23. PMID 15687232

12. Lenz G, Dreyling M, Schiegnitz E et al. Myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission prolongs progression free survival in follicular lymphoma: results of a prospective, randomized trial of the German Low Grade Lymphoma Study Group. Blood 2004; 104(9):2667-74. PMID 15238420
13. Schouten HC, Qian W, Kvaloy S et al. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP trial. J Clin Oncol 2003; 21(21):3918-27. PMID 14517188
14. Bozkaya Y, Uncu D, Dagdas S, et al. Evaluation of lymphoma patients receiving high-dose therapy and autologous stem cell transplantation: experience of a single center. Indian J Hematol Blood Transfus. Sep 2017;33(3):361-369. PMID 28824238
15. Jimenez-Ubieto A, Grande C, Caballero D, et al. Autologous stem cell transplantation may be curative for patients with follicular lymphoma with early therapy failure who reach complete response after rescue treatment. Hematol Oncol. 2018 Dec;36(5). PMID 30129233
16. International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993; 329(14):987-94. PMID 8141877
17. Solal-Celigny P, Roy P, Colombat P et al. Follicular lymphoma international prognostic index. Blood 2004; 104(5):1258-65. PMID 15126323
18. Greb A, Bohlius J, Schiefer D, et al. High-dose chemotherapy with autologous stem cell transplantation in the first-line treatment of aggressive non-Hodgkin lymphoma (NHL) in adults. Cochrane Database Syst Rev. Jan 23 2008(1): CD004024. PMID 18254036
19. Haioun C, Lepage E, Gisselbrecht C et al. Benefit of autologous bone marrow transplantation over sequential chemotherapy in poor-risk aggressive non-Hodgkin's lymphoma: updated results of the prospective study LNH87-2. Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 1997; 15(3):1131-7. PMID 9060555
20. Kaiser U, Uebelacker I, Abel U et al. Randomized study to evaluate the use of high-dose therapy as part of primary treatment for "aggressive" lymphoma. J Clin Oncol 2002; 20(22):4413-9. PMID 12431962
21. Kluin-Nelemans HC, Zagonel V, Anastasopoulou A et al. Standard chemotherapy with or without high-dose chemotherapy for aggressive non-Hodgkin's lymphoma: randomized phase III EORTC study. J Natl Cancer Inst 2001; 93(1):22-30. PMID 11136838
22. Sweetenham JW, Santini G, Qian W et al. High-dose therapy and autologous stem-cell transplantation versus conventional-dose consolidation/maintenance therapy as post-remission therapy for adult patients with lymphoblastic lymphoma: results of a randomized trial of the European Group for Blood and Marrow Transplantation and the United Kingdom Lymphoma Group. J Clin Oncol 2001; 19(11):2927-36. PMID 11387366
23. Fisher RI. Autologous stem-cell transplantation as a component of initial treatment for poor-risk patients with aggressive non-Hodgkin's lymphoma: resolved issues versus remaining opportunity. J Clin Oncol 2002; 20(22):4411-2. PMID 12431961
24. Haioun C, Lepage E, Gisselbrecht C et al. Survival benefit of high-dose therapy in poor-risk aggressive non-Hodgkin's lymphoma: final analysis of the prospective LNH87-2 protocol--a Groupe d'Etude des Lymphomes de l'Adulte study. J Clin Oncol 2000; 18(16):3025-30. PMID 10944137
25. Fisher RI. Autologous bone marrow transplantation for aggressive non-Hodgkin's lymphoma: lessons learned and challenges remaining. J Natl Cancer Inst 2001; 93(1):4-5. PMID 11136829

26. Hahn T, Wolff SN, Czuczman M et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of diffuse large cell B-cell non-Hodgkin's lymphoma: an evidence-based review. Biol Blood Marrow Transplant 2001; 7(6):308-31. PMID 11464975
27. Kimby E, Brandt L, Nygren P et al. A systematic overview of chemotherapy effects in aggressive non-Hodgkin's lymphoma. Acta Oncol 2001; 40(3-Feb):198-212. PMID 11441932
28. Philip T, Biron P. High-dose chemotherapy and autologous bone marrow transplantation in diffuse intermediate- and high-grade non-Hodgkin lymphoma. Crit Rev Oncol Hematol 2002; 41(2):213-23. PMID 11856597
29. Betticher DC, Martinelli G, Radford JA et al. Sequential high dose chemotherapy as initial treatment for aggressive sub-types of non-Hodgkin lymphoma: results of the international randomized phase III trial (MISTRAL). Ann Oncol 2006; 17(10):1546-52. PMID 16888080
30. Baldissera RC, Nucci M, Vigorito AC et al. Frontline therapy with early intensification and autologous stem cell transplantation versus conventional chemotherapy in unselected high-risk, aggressive non-Hodgkin's lymphoma patients: a prospective randomized GEMOH report. Acta Haematol 2006; 115(1-2):15-21. PMID 16424644
31. Olivieri A, Santini G, Patti C et al. Upfront high-dose sequential therapy (HDS) versus VACOP-B with or without HDS in aggressive non-Hodgkin's lymphoma: long-term results by the NHLCSG. Ann Oncol 2005; 16(12):1941-8. PMID 16157621
32. Stiff PJ, Unger JM, Cook JR, et al. Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. N Engl J Med. Oct 31 2013;369(18):1681-1690. PMID 24171516
33. Casasnovas RO, Ysebaert L, Thieblemont C, et al. FDG-PET-driven consolidation strategy in diffuse large B-cell lymphoma: final results of a randomized phase 2 study. *Blood.* Sep 14 2017;130(11):1315-1326. PMID 28701367
34. Strüßmann T, Fritsch K, Baumgarten A, et al. Favourable outcomes of poor prognosis diffuse large B-cell lymphoma patients treated with dose-dense rituximab, high-dose methotrexate and six cycles of CHOP-14 compared to first-line autologous transplantation. Br J Haematol. Sep 2017;178(6):927-935. PMID 28643323
35. Qualls D, Sullivan A, Li S, et al. High-dose thiotepa, busulfan, cyclophosphamide, and autologous stem cell transplantation as upfront consolidation for systemic non-Hodgkin lymphoma with synchronous central nervous system involvement. Clin Lymphoma Myeloma Leuk. Dec 2017;17(12):884-888. PMID 28870642
36. Jaffe ES. The 2008 WHO classification of lymphomas: implications for clinical practice and translational research. *Hematology Am Soc Hematol Educ Program.* Dec 2009:523-531. PMID 20008237
37. Philip T, Guglielmi C, Hagenbeek A et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin’s lymphoma. N Engl J Med 1995; 333(23):1540-5. PMID 7477169
38. Fujita N, Kobayashi R, Atsuta Y et al. Hematopoietic stem cell transplantation in children and adolescents with relapsed or refractory B-cell non-Hodgkin lymphoma. Int. J. Hematol. 2019 Apr;109(4). PMID 30701466
39. Monjanel H, Deconinck E, Perrodeau E et al. Long-term follow-up of tandem high-dose therapy with autologous stem cell support for adults with high-risk age-adjusted international prognostic index aggressive non-Hodgkin lymphomas: A GOELAMS pilot study. Biol Blood Marrow Transplant 2011; 17(6):935-40. PMID 21109011

40. Papadopoulos KP, Noguera-Irizarry W, Wiebe L et al. Pilot study of tandem high-dose chemotherapy and autologous stem cell transplantation with a novel combination of regimens in patients with poor risk lymphoma. Bone Marrow Transplant 2005; 36(6):491-7. PMID 16044139
41. Tarella C, Zanni M, Di Nicola M et al. Prolonged survival in poor-risk diffuse large B-cell lymphoma following front-line treatment with rituximab-supplemented, early-intensified chemotherapy with multiple autologous hematopoietic stem cell support: a multicenter study by GITIL (Gruppo Italiano Terapie Innovative nei Linfomi). Leukemia 2007; 21(8):1802-11. PMID 17554382
42. Satwani P, Jin Z, Martin PL, et al. Sequential myeloablative autologous stem cell transplantation and reduced intensity allogeneic hematopoietic cell transplantation is safe and feasible in children, adolescents and young adults with poor-risk refractory or recurrent Hodgkin and non-Hodgkin lymphoma. Leukemia. Feb 2015; 29(2): 448-55. PMID 24938649
43. Banks PM, Chan J, Cleary ML et al. Mantle cell lymphoma. A proposal for unification of morphologic, immunologic, and molecular data. Am J Surg Pathol 1992; 16(7):637-40. PMID 1530105
44. Hoster E, Dreyling M, Klapper W et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood 2008; 111(2):558-65. PMID 17962512
45. Dreyling M, Lenz G, Hoster E et al. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL network. Blood 2005; 105(7):2677-84. PMID 15591112
46. Zoellner AK, Unterhalt M, Stilgenbauer S, et al. Long-term survival of patients with mantle cell lymphoma after autologous haematopoietic stem-cell transplantation in first remission: a post-hoc analysis of an open-label, multicentre, randomised, phase 3 trial. Lancet Haematol. Sep 2021; 8(9): e648-e657. PMID 34450102
47. Till BG, Gooley TA, Crawford N et al. Effect of remission status and induction chemotherapy regimen on outcome of autologous stem cell transplantation for mantle cell lymphoma. Leuk Lymphoma 2008; 49(6):1062-73. PMID 18452065
48. Garcia-Noblejas A, Cannata-Ortiz J, Conde E, et al. Autologous stem cell transplantation (ASCT) in patients with mantle cell lymphoma: a retrospective study of the Spanish lymphoma group (GELTAMO). *Ann Hematol.* Aug 2017;96(8):1323-1330. PMID 28536895
49. Metzner B, Müller TH, Casper J, et al. Long-term outcome in patients with mantle cell lymphoma following high-dose therapy and autologous stem cell transplantation. Eur J Haematol. Aug 2023;111(2): 220-228. PMID 37094812
50. Villanueva ML, Vose JM. The role of hematopoietic stem cell transplantation in non-Hodgkin lymphoma. Clin Adv Hematol Oncol 2006; 4(7):521-30. PMID 17147239
51. Khouri IF, Lee MS, Saliba RM et al. Nonablative allogeneic stem-cell transplantation for advanced/recurrent mantle-cell lymphoma. J Clin Oncol 2003; 21(23):4407-12. PMID 14645431
52. Maris MB, Sandmaier BM, Storer BE et al. Allogeneic hematopoietic cell transplantation after fludarabine and 2 Gy total body irradiation for relapsed and refractory mantle cell lymphoma. Blood 2004; 104(12):3535-42. PMID 15304387
53. Kruger WH, Hirt C, Basara N, et al. Allogeneic stem cell transplantation for mantle cell lymphoma-update of the prospective trials of the East German Study Group

Hematology/Oncology (OSHO#60 and #74). Ann Hematol. Jun 2021; 100(6): 1569-1577. PMID 33829299
54. Tam CS, Bassett R, Ledesma C et al. Mature results of the MD Anderson Cancer Center risk-adapted transplantation strategy in mantle cell lymphoma. Blood 2009; 113(18):4144-52. PMID 19168784
55. Geisler C. Mantle cell lymphoma: are current therapies changing the course of the disease? Curr Oncol Rep 2009; 11(5):371-7. PMID 19679012
56. Zhai Y, Wang J, Jiang Y, et al. The efficiency of autologous stem cell transplantation as the first-line treatment for nodal peripheral T-cell lymphoma: results of a systematic review and meta-analysis. Expert Rev Hematol. Mar 2022; 15(3): 265-272. PMID 35152814
57. Schmitz N, Truemper L, Bouabdallah K, et al. A randomized phase 3 trial of autologous vs allogeneic transplantation as part of first-line therapy in poor-risk peripheral T-NHL. Blood. May 13 2021; 137(19): 2646-2656. PMID 33512419
58. Reimer P, Rüdiger T, Geissinger E, et al. Autologous stem-cell transplantation as first-line therapy in peripheral T-cell lymphomas: results of a prospective multicenter study. J Clin Oncol 2009; 27(1):106-13. PMID 19029417
59. Corradini P, Tarella C, Zallio F et al. Long-term follow-up of patients with peripheral T-cell lymphoma treated up-front with high-dose chemotherapy followed by autologous stem cell transplantation. Leukemia 2006; 20(9):1533-8. PMID 16871285
60. Mercadal S, Briones J, Xicoy B et al. Intensive chemotherapy (high-dose CHOP/ESHAP regimen) followed by autologous stem-cell transplantation in previously untreated patients with peripheral T-cell lymphoma. Ann Oncol 2008; 19(5):958-63. PMID 18303032
61. Rodriguez J, Conde E, Gutierrez A et al. Frontline autologous stem cell transplantation in high-risk peripheral T-cell lymphoma: a prospective study from The Gel-Tamo Study Group. Eur J Haematol 2007; 79(1):32-8. PMID 17598836
62. Wang J, Wei L, Ye J, et al. Autologous hematopoietic stem cell transplantation may improve long-term outcomes in patients with newly diagnosed extranodal natural killer/T-cell lymphoma, nasal type: a retrospective controlled study in a single center. *Int J Hematol.* Jan 2018;107(1):98-104. PMID 28856590
63. Wu M, Wang F, Zhao S, et al. Autologous hematopoietic stem cell transplantation improves survival outcomes in peripheral T-cell lymphomas: a multicenter retrospective real-world study. Ann Hematol. Nov 2023; 102(11): 3185-3193. PMID 37700194
64. Mamez AC, Dupont A, Blaise D, et al. Allogeneic stem cell transplantation for peripheral T cell lymphomas: a retrospective study in 285 patients from the Societe Francophone de Greffe de Moelle et de Therapie Cellulaire (SFGM-TC). J Hematol Oncol. May 19 2020; 13(1): 56. PMID 32429979
65. Du J, Yu D, Han X, et al. Comparison of Allogeneic Stem Cell Transplant and Autologous Stem Cell Transplant in Refractory or Relapsed Peripheral T-Cell Lymphoma: A Systematic Review and Meta-analysis. JAMA Netw Open. May 03 2021; 4(5): e219807. PMID 34042995
66. Song KW, Mollee P, Keating A et al. Autologous stem cell transplant for relapsed and refractory peripheral T-cell lymphoma: variable outcome according to pathological subtype. Br J Haematol 2003; 120(6):978-85. PMID 12648067
67. Rodriguez J, Conde E, Gutierrez A et al. The adjusted International Prognostic Index and beta-2-microglobulin predict the outcome after autologous stem cell transplantation in relapsing/refractory peripheral T-cell lymphoma. Haematologica 2007; 92(8):1067-74. PMID 17640855

68. Kyriakou C, Canals C, Finke J et al. Allogeneic stem cell transplantation is able to induce long-term remissions in angioimmunoblastic T-cell lymphoma: a retrospective study from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 2009; 27(24):3951-8. PMID 19620487
69. Klebaner D, Koura D, Tzachanis D, et al. Intensive Induction Therapy Compared With CHOP for Hepatosplenic T-cell Lymphoma. Clin Lymphoma Myeloma Leuk. Jul 2020; 20(7): 431-437.e2. PMID 32284297
70. Rashidi A, Cashen AF. Outcomes of allogeneic stem cell transplantation in hepatosplenic T-cell lymphoma. Blood Cancer J. Jun 05 2015; 5(6): e318. PMID 26047388
71. Voss MH, Lunning MA, Maragulia JC, et al. Intensive induction chemotherapy followed by early high-dose therapy and hematopoietic stem cell transplantation results in improved outcome for patients with hepatosplenic T-cell lymphoma: a single institution experience. Clin Lymphoma Myeloma Leuk. Feb2013; 13(1): 8-14. PMID 23107915
72. Tanase A, Schmitz N, Stein H, et al. Allogeneic and autologous stem cell transplantation for hepatosplenic T-cell lymphoma: a retrospective study of the EBMT Lymphoma Working Party. Leukemia. Mar 2015; 29(3): 686-8. PMID 25234166
73. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: B-Cell Lymphomas. Version 2.2024; https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed May 16, 2024.
74. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: T-Cell Lymphomas. Version 3.2024; https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf. Accessed May 16, 2024.
75. Munshi PN, Hamadani M, Kumar A, et al. ASTCT, CIBMTR, and EBMT clinical practice recommendations for transplant and cellular therapies in mantle cell lymphoma. Bone Marrow Transplant. Dec 2021; 56(12): 2911-2921.PMID 34413469
76. Epperla N, Kumar A, Abutalib SA, et al. ASTCT Clinical Practice Recommendations for Transplantation and Cellular Therapies in Diffuse Large B Cell Lymphoma. Transplant Cell Ther. Sep 2023; 29(9): 548-555. PMID 37419325
77. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Stem Cell Transplantation (Formerly 110.8.1) (110.23). 2016; https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=366&ncdver=1&DocID=110.23&list_type=ncd&bc=gAAAAAgAAAAAAA%3d%3d&. Accessed May 16, 2024.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through May 16, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/13	10/16/12	10/16/12	• Topic split out from former combined bone marrow transplant policies. • Policy formatted to mirror BCBSA. • Added “relative contraindications” to inclusionary/exclusionary section. • Removed deleted codes G0265, G0266 and G0267.
3/1/14	12/10/13	1/6/14	• Updated policy to reflect BCBSA updates in inclusionary/ exclusionary guidelines
7/1/15	4/24/15	5/8/15	Routine maintenance
7/15/16	4/19/16	4/19/16	Routine approval
7/1/17	4/18/17	4/18/17	Routine maintenance Added revised WHO classification Medicare NCD updated Added procedure code 38207
7/1/18	4/17/18	4/17/18	• Routine maintenance • 38220 and 38221 deleted based on nomenclature changes – for diagnostic purposes only
7/1/19	4/16/19	4/16/19	• Routine maintenance
11/1/19	8/20/19		• Routine maintenance
11/1/20	8/18/20		• Routine maintenance
11/1/21	8/17/21		• Routine maintenance
11/1/22	8/16/22		• Routine maintenance
11/1/23	8/15/23		• Routine maintenance (slp) • Vendor Managed: N/A
11/1/24	8/20/24		• Routine maintenance (slp) • Vendor Managed: N/A • S2140 and S2142 moved to EST • Clarification that “IPI score will not be a necessary requirement for primary CNS diffuse large B-cell lymphoma” added to inclusions

Next Review Date: 3rd Qtr, 2024

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: BMT - HEMATOPOIETIC CELL TRANSPLANTATION FOR NON-HODGKIN LYMPHOMAS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply. For an approved, preauthorized transplant, BCN will cover the necessary hospital, surgical, lab and X-ray services for a non-member donor, including charges for donating the bone marrow, under the BCN member's certificate, unless the non-member donor has coverage for such services. This also includes solid organ donor procurement fees. Donor travel, meals and lodging expenses are *not* covered unless the BCN member has a rider that covers such services. BCN does NOT cover expenses incurred by a BCN member for donating bone marrow, stem cells or a solid organ (e.g., kidney, liver lobe, lung lobe) to a non-BCN member. The donor services would be considered not medically necessary for the BCN member.
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member’s certificate and is not guaranteed. Please consult the individual member’s certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.