

Protocol

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

(80120)

(Formerly Hematopoietic Stem Cell Transplantation for Non-Hodgkin Lymphomas)

Medical Benefit		Effective Date: 04/01/13	Next Review Date: 05/19
Preauthorization	Yes	Review Dates: 04/07, 05/08, 05/09, 05/10, 05/11, 05/12, 05/13, 05/14, 05/15, 05/16, 05/17, 05/18	

Preauthorization is required and must be obtained through Case Management.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> With indolent B-cell non-Hodgkin lymphomas 	Interventions of interest are: <ul style="list-style-type: none"> Autologous hematopoietic cell transplantation as first line therapy 	Comparators of interest are: <ul style="list-style-type: none"> Standard care 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Change in disease status Morbid events Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With aggressive B-cell non-Hodgkin lymphomas, excluding mantle cell lymphoma 	Interventions of interest are: <ul style="list-style-type: none"> Autologous hematopoietic cell transplantation as consolidation therapy after first complete remission 	Comparators of interest are: <ul style="list-style-type: none"> Standard care 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Change in disease status Morbid events Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With non-Hodgkin lymphomas, excluding mantle cell lymphoma 	Interventions of interest are: <ul style="list-style-type: none"> Tandem autologous and allogeneic hematopoietic cell transplantation 	Comparators of interest are: <ul style="list-style-type: none"> Standard care 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Change in disease status Morbid events Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With mantle cell lymphoma 	Interventions of interest are: <ul style="list-style-type: none"> Autologous, allogeneic, or tandem hematopoietic cell transplantation 	Comparators of interest are: <ul style="list-style-type: none"> Standard care 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Change in disease status Morbid events Treatment-related mortality Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> • With peripheral T-cell lymphoma 	Interventions of interest are: <ul style="list-style-type: none"> • Autologous or allogeneic hematopoietic cell transplantation 	Comparators of interest are: <ul style="list-style-type: none"> • Standard care 	Relevant outcomes include: <ul style="list-style-type: none"> • Overall survival • Disease-specific survival • Change in disease status • Morbid events • Treatment-related mortality • Treatment-related morbidity

DESCRIPTION

Hematopoietic cell transplantation (HCT) refers to a procedure by which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs, with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although umbilical cord blood is an allogeneic source, the stem cells in it are antigenically “naive” and thus are associated with a lower incidence of rejection or graft-versus-host disease. Umbilical cord blood is discussed in greater detail in the Placental and Umbilical Cord Blood as a Source of Stem Cells Protocol.

SUMMARY OF EVIDENCE

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

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

For individuals who have mantle cell lymphoma who receive autologous, allogeneic, or tandem HCT, the evidence includes case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. Due in part to the rarity of this disease,

randomized trials on the use of HCT for MCL have not been conducted. Case series have shown long-term disease control of this aggressive lymphoma with autologous HCT (with rituximab) to consolidate a first remission; however, the use of autologous HCT in the relapsed setting has not shown improved outcomes. Allo-HCT has shown prolonged disease control in the relapsed or refractory setting. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have peripheral T-cell lymphoma (PTCL) who receive autologous HCT or allo-HCT, the evidence includes prospective trials and case reports. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. The role of HCT in PTCL is not well-defined. Few studies have been conducted, and most were performed retrospectively, with a limited number of patients; moreover, the patient populations were heterogeneous and included good- and poor-risk patients in the same study. Patient population and characteristics of the studies can be explained partially by the rarity and heterogeneity of the particular group of lymphomas addressed. Additionally, studies of this nature often mix three types of patients: one type of patient has PTCL not otherwise specified, which has a poorer prognosis; another type has anaplastic lymphoma kinase-positive anaplastic large-cell lymphomas, which has a better prognosis—even with conventional chemotherapy regimens; and a third type has anaplastic lymphoma kinase-negative anaplastic large-cell lymphomas, which has a worse prognosis than anaplastic lymphoma kinase-positive anaplastic large-cell lymphomas (but better than patients with PTCL not otherwise specified). There have been no randomized studies comparing chemotherapy regimens solely in patients with PTCL (i.e., some randomized studies have included PTCL with aggressive B-cell lymphomas). For first-line therapy, results from recent phase 2 studies with autologous HCT as consolidation offers the best survival outcomes for patients with high-risk features; randomized trials to confirm this have not been performed. No relevant data for the use of allogeneic HCT in the first-line setting are available. Patients with relapsed or refractory PTCL are generally considered incurable with chemotherapy alone. In the salvage setting, data have shown that the use of HCT may improve survival outcomes similar to the results seen in corresponding aggressive B-cell lymphomas in the same treatment setting. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

POLICY

For patients with non-Hodgkin lymphoma (NHL) B-cell subtypes considered aggressive (except mantle cell lymphoma), either allogeneic hematopoietic cell transplantation (HCT) using a myeloablative conditioning regimen or autologous HCT may be considered **medically necessary**:

- as salvage therapy for patients who do not achieve a complete remission (CR) after first-line treatment (induction) with a full course of standard-dose chemotherapy;
- to achieve or consolidate a CR for those in a chemo-sensitive first or subsequent relapse; or
- to consolidate a first CR in patients with diffuse large B-cell lymphoma, with an age-adjusted International Prognostic Index score that predicts a high- or high-intermediate risk of relapse.

For patients with mantle cell lymphoma:

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

For patients with NHL B-cell subtypes considered indolent, either allogeneic HCT using a myeloablative conditioning regimen or autologous HCT may be considered **medically necessary**:

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

Either autologous HCT or allogeneic HCT is considered **investigational**:

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

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

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

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

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

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

POLICY GUIDELINES

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

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

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

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

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

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

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

High-risk (aggressive) T-cell and natural killer (NK) cell neoplasms: the T-cell and NK cell neoplasms are a clinically heterogeneous group of rare disorders, most of which have an aggressive clinical course and poor prognosis. The exception includes the following subtypes, which typically have a relatively indolent and protracted course: T-cell large granulocyte leukemia (T-LGL), chronic lymphoproliferative disorder of NK cells, early-stage mycosis fungoides, primary cutaneous anaplastic large-cell lymphoma (ALCL), and anaplastic lymphoma kinase-anaplastic large-cell lymphomas (ALK+ ALCL).¹

MEDICARE ADVANTAGE

If a transplant is needed, we arrange to have the transplant center review and decide whether the patient is an appropriate candidate for the transplant.

BACKGROUND

NON-HODGKIN LYMPHOMA

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

European and American pathologists proposed a new classification, the Revised European-American Lymphoma (REAL) Classification² 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 table below contains the most recent lymphoma classification, the 2016 World Health Organization classification.⁴

Table 1. Updated WHO Classification (2016)

Classification of Neoplasms
Mature B-cell neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis ^a
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic lymphoma/leukemia, unclassifiable
<ul style="list-style-type: none"> • Splenic diffuse red pulp small B-cell lymphoma • Hairy cell leukemia-variant
Lymphoplasmacytic lymphoma
<ul style="list-style-type: none"> • Waldenström macroglobulinemia
Monoclonal gammopathy of undetermined significance, IgM ^a
Heavy chain diseases
<ul style="list-style-type: none"> • Alpha heavy chain disease • Gamma heavy chain disease • Mu heavy chain disease
Monoclonal gammopathy of undetermined significance, IgG/IgA ^a
Plasma cell myeloma
Solitary plasmacytoma of bone
Extrasosseous plasmacytoma
Monoclonal immunoglobulin deposition diseases ^a
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma (MZL)
<ul style="list-style-type: none"> • Pediatric nodal MZL
Follicular lymphoma
<ul style="list-style-type: none"> • In situ follicular neoplasia^a • Duodenal-type follicular lymphoma^a
Pediatric type follicular lymphoma ^a
<ul style="list-style-type: none"> • Large B-cell lymphoma with IRF4 rearrangement^a
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
<ul style="list-style-type: none"> • In situ mantle cell neoplasia^a
Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS)
<ul style="list-style-type: none"> • Germinal center B-cell type^a • Activated B-cell type^a
T-cell/histiocyte-rich large B-cell lymphoma
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
Primary cutaneous DLBCL, leg type
ALK [anaplastic lymphoma kinase]-positive large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
HHV8 DLBCL NOS ^a
Burkitt lymphoma
Burkitt-like lymphoma with 11q aberration ^a
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements ^a
High-grade B-cell lymphoma, NOS ^a
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma
Mature T-cell and NK-cell neoplasms

Classification of Neoplasms

T-cell prolymphocytic leukemia
 T-cell large granular lymphocytic leukemia
 Chronic lymphoproliferative disorder of NK cells
 Aggressive NK-cell leukemia
 Systemic Epstein-Barr virus-positive T-cell lymphoproliferative of childhood^a
 Hydroa vacciniforme-like lymphoproliferative disorder^a
 Adult T-cell leukemia/ lymphoma
 Extranodal NK/T-cell lymphoma, nasal type
 Enteropathy-associated T-cell lymphoma
 Monomorphic epitheliotropic intestinal T-cell lymphoma^a
 Indolent T-cell lymphoproliferative disorder of the GI tract^a
 Hepatosplenic T-cell lymphoma
 Subcutaneous panniculitis-like T-cell lymphoma
 Mycosis fungoides
 Sézary syndrome
 Primary cutaneous CD30-positive T-cell lymphoproliferative disorder

- Lymphomatoid papulosis
- Primary cutaneous anaplastic large-cell lymphoma

Primary cutaneous gamma-delta T-cell lymphoma
 Primary cutaneous aggressive epidermotropic CD8-positive cytotoxic T-cell lymphoma^a
 Primary cutaneous acral CD8+ T-cell lymphoma^a
 Primary cutaneous small/medium CD4-positive T-cell lymphoproliferative disorder^a
 Peripheral T-cell lymphoma, NOS
 Angioimmunoblastic T-cell lymphoma
 Follicular T-cell lymphoma^a
 Nodal peripheral T-cell lymphoma with TFH phenotype^a
 Anaplastic large-cell lymphoma (ALCL), ALK-positive
 Anaplastic large-cell lymphoma (ALCL), ALK-negative^a
 Breast implant-associated anaplastic large-cell lymphoma^a

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

^aChanges from 2008 WHO classification. Provisional entities are listed in italics.

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

The International Lymphoma Classification Project identified the most common NHL subtypes as follows: diffuse large B-cell lymphoma (DLBCL) 31%, follicular lymphoma 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.⁵

Types of NHL

In general, NHL can be divided into two prognostic groups, indolent and aggressive. Indolent NHL has a relatively good prognosis, with a median survival of 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.¹ Although indolent NHL is responsive to radiotherapy and chemotherapy, a continuous rate of relapse is seen in advanced stages.¹ These patients can often be treated again if their disease remains of the indolent type. Indolent NHL may transform into a more aggressive form, which is generally treated with regimens that are used for aggressive, recurrent NHL. Histologic transformation to higher grade lymphoma occurs in up to 70% of patients with low-grade lymphoma,⁶ and median survival with conventional chemotherapy is one year or less.

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

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

Risk Assessment

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

Based on the following five risk factors prognostic of overall survival and adjusted for patient age, the IPI defines four 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 one 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 two or more risk factors have a less than 50% chance of relapse-free survival and overall survival at five years. Age-adjusted IPI and stage-adjusted modifications of this IPI are used for younger patients with localized disease.

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

With the success of the IPI, a separate prognostic index was developed for follicular lymphoma, which has multiple independent risk factors for relapse after first complete remission. The proposed and validated Follicular Lymphoma International Prognostic Index contains five 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 four lymph node areas involved
5. Elevated serum LDH level.

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

Mantle Cell Lymphomas

MCL comprises 65% to 68% of NHL and has been recognized for some time now as a unique lymphoma subtype with a particularly aggressive course. MCL is characterized by a chromosomal translocation t(11;14), and the term mantle cell lymphoma was proposed in 1992 by Banks et al.⁹ The number of therapeutic trials is not as

numerous for MCL as for other NHL, because it was not widely recognized until the REAL classification. MCL shows a strong predilection for senior men, and most cases (70%) present with disseminated (stage IV) disease; extranodal involvement is common. Localized MCL is quite rare. MCL has a median survival of approximately two to four years, and although most patients achieve remission with first-line therapy, relapse inevitably occurs—often within 12 to 18 months. MCL is rarely, if ever, cured with conventional therapy, and no standardized therapeutic approach to MCL is used.

Risk Assessment

Not until recently has a prognostic index been established for patients with MCL. Application of the IPI or Follicular Lymphoma International Prognostic Index system to patients with MCL has shown limitations, which included no separation of some important risk groups. In addition, some of the individual IPI and Follicular Lymphoma International Prognostic Index risk factors, including number of extranodal sites and number of involved nodal areas, showed no prognostic relevance, and hemoglobin showed no independent prognostic relevance in patients with MCL.¹⁰ Therefore, a new prognostic index for patients with MCL was developed and should prove useful in comparing clinical trial results for MCL.

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

1. Age
2. ECOG Performance Status
3. Serum LDH (calculated as a ratio of LDH to a laboratory's upper limit of normal)
4. White blood cell (WBC) count
 - Zero points each are assigned to age younger than 50 years, ECOG Performance Status score of 0-1, LDH ratio of less than 0.67 U/L, WBC of less than 6700/ μ L
 - One point each for age 50 to 59 years, LDH ratio of 0.67-0.99 U/L, WBC of 6700-9999/ μ L
 - Two points each for age 60 to 69 years, ECOG Performance Status score of 2-4, LDH ratio of 1.00-1.49 U/L, WBC of 10,000-14,999/ μ L
 - Three points each for age 70 years or older, LDH ratio of 1.5 U/L or greater, WBC of 15,000/ μ L or more.

MCL International Prognostic Index allows separation of three groups with significantly different prognoses¹⁰:

- Zero to three points denotes low-risk, which affects 44% of patients, who have a five year overall survival rate of 60% (median overall survival, not reached)
- Four to five points denotes intermediate risk, which affects 35% of patients, who have a median overall survival of 51 months
- Six to 11 points denotes high-risk, which affects 21% of patients, who have a median overall survival of 29 months

Peripheral T-Cell Lymphoma

Most PTCLs are aggressive and fall into the categories of PTCL, not otherwise specified (PTCL-NOS), angio-immunoblastic lymphoma and anaplastic large-cell lymphoma which, when 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 five years with standard chemotherapy regimens range from 20% to 35%. The poor results with conventional chemotherapy have prompted exploration of the role of hematopoietic cell transplantation (HCT) as therapy.

Staging

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

Table 2. Ann Arbor Classification

Stage	Involvement
I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of extralymphatic organ or site and one or more lymph node regions on the same side of the diaphragm (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of extralymphatic organ or site (IIIE) or by involvement of the spleen (IIIS) or both (IIISE)
IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement

Treatment for NHL

Hematopoietic Cell Transplantation

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

CONVENTIONAL PREPARATIVE CONDITIONING FOR HCT

The conventional practice of allogeneic HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation; this is performed at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect of this procedure is due to a combination of initial eradication of malignant cells and the subsequent graft-versus-malignancy effect that is mediated by non-self-immunologic effector cells that develop after engraftment of allogeneic stem cells within the patient's bone marrow space. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are medically fit to tolerate substantial adverse events that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease, which also increase susceptibility to opportunistic infections. The immune reactivity between donor T cells and malignant cells is responsible for the graft-versus-malignancy effect; it also leads to acute and chronic graft-versus-host disease.

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

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HCT

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of

cytotoxic drugs or radiotherapy that are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is two-fold: to reduce disease burden, and to minimize treatment-related morbidity and nonrelapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of nonrelapse mortality and relapse due to residual disease. RIC regimens can be viewed as a continuum—from nearly total myeloablative to minimal myeloablative with lymphoablation—because it tailors its intensity to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For the purposes of this protocol, reduced-intensity conditioning refers to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (traditional) regimens.

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.

RELATED PROTOCOLS

Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Hematopoietic Cell Transplantation for Primary Amyloidosis

Hematopoietic Cell Transplantation for Waldenström Macroglobulinemia

Placental and Umbilical Cord Blood as a Source of Stem Cells

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

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

REFERENCES

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

1. National Cancer Institute. Adult Non-Hodgkin Lymphoma Treatment (PDQ®)—Health Professional Version. 2017; <http://www.cancer.gov/cancertopics/pdq/treatment/adult-non-hodgkins/healthprofessional>. Accessed January 2, 2018.

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