

Policy #: 143

Original policy date: 10/19/07
Revised date: 07/28/09

Page: 1 of 11

Title

Hematopoietic Stem Cell Transplantation for Non-Hodgkin Lymphomas

Description

Hematopoietic Stem-Cell Transplantation¹

Hematopoietic stem-cell transplantation (SCT) refers to a procedure in 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 radiation therapy. Bone-marrow stem cells may be obtained from the transplant recipient (i.e., autologous SCT) or from a donor (i.e., allogeneic SCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD). Immunologic compatibility between infused stem cells and the recipient is not an issue in autologous SCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic SCT. Compatibility is established by typing human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA A, B, and DR loci on each leg of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

Conventional Preparative Conditioning for Hematopoietic SCT

The conventional practice of allogeneic SCT involves administration of myelotoxic agents (e.g., cyclophosphamide, busulfan) with or without total-body irradiation at doses sufficient to cause bone marrow failure. The beneficial treatment effect in this procedure results from chemotherapeutic eradication of malignant cells with an associated immune-mediated graft-versus-malignancy effect. While such treatment may eliminate the malignant cells, patients are as likely to die from opportunistic infections, graft-versus-host disease (GVHD), and/or organ failure as from the underlying malignancy.

Autologous SCT necessitates myeloablative chemotherapy to eradicate cancerous cells from the blood and bone marrow, thus permitting subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic progenitor cells. As a consequence, autologous SCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous SCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

Reduced-Intensity Conditioning for Allogeneic SCT

Reduced-intensity conditioning (RIC) refers to chemotherapy regimens that seek to reduce adverse effects secondary to bone marrow toxicity, while retaining the beneficial graft-versus-malignancy effect of allogeneic transplantation. These regimens do not initially eradicate the patient’s hematopoietic ability, allowing relatively prompt hematopoietic recovery (e.g., 28 days or less) even without a transplant. Patients who undergo RIC with allogeneic SCT 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. A number of different cytotoxic regimens, with or without radiotherapy, may

be used for RIC allotransplantation. They represent a continuum in their effects, from nearly totally myeloablation, to minimal myeloablation with lymphoablation.

Non-Hodgkin Lymphoma (NHL)

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 (WF) was developed to unify different classification systems into one. (1) The WF divided NHL into low-, intermediate-, and high-grade, with subgroups based on histologic cell type. Since 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 WF 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 (WHO) classification. (3) The WHO/REAL classification recognizes 3 major categories of lymphoid malignancies based on morphology and cell lineage: B-cell neoplasms, T-cell/natural killer (NK)-cell neoplasms, and Hodgkin lymphoma.

Within the B-cell and T-cell categories, two subdivisions are recognized: precursor neoplasms, which correspond to the earliest stages of differentiation, and more mature differentiated neoplasms.

Updated REAL/WHO Classification

B-Cell Neoplasms

1. Precursor B-cell neoplasm: precursor B-acute lymphoblastic leukemia/lymphoblastic lymphoma (LBL).
2. Peripheral B-cell neoplasms
 1. B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma*
 2. B-cell prolymphocytic leukemia
 3. Lymphoplasmacytic lymphoma/immunocytoma*
 4. Mantle cell lymphoma (MCL)
 5. Follicular lymphoma
 6. Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphatic tissue (MALT) type
 7. Nodal marginal zone B-cell lymphoma (+/- monocytoid B-cells)
 8. Splenic marginal zone lymphoma (+/- villous lymphocytes)
 9. Hairy-cell leukemia
 10. Plasmacytoma/plasma cell myeloma
 11. Diffuse large B-cell lymphoma
 12. Burkitt lymphoma

T-Cell and Putative NK-Cell Neoplasms

1. Precursor T-cell neoplasm: precursor T-acute lymphoblastic leukemia/LBL
2. Peripheral T-cell (PTCL) and NK-cell neoplasms
 1. T-cell chronic lymphocytic leukemia/prolymphocytic leukemia
 2. T-cell granular lymphocytic leukemia
 3. Mycosis fungoides/Sézary syndrome
 4. Peripheral T-cell lymphoma, not otherwise characterized
 5. Hepatosplenic gamma/delta T-cell lymphoma
 6. Subcutaneous panniculitis-like T-cell lymphoma
 7. Angioimmunoblastic T-cell lymphoma
 8. Extranodal T-/NK-cell lymphoma, nasal type
 9. Enteropathy-type intestinal T-cell lymphoma
 10. Adult T-cell lymphoma/leukemia (human T-lymphotrophic virus [HTLV] 1+)
 11. Anaplastic large cell lymphoma, primary systemic type
 12. Anaplastic large cell lymphoma, primary cutaneous type

13. Aggressive NK-cell leukemia

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

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

Several subtypes of NHL have emerged with the REAL/WHO classification with unique clinical and biologic features, and they will be addressed separately throughout the policy, when necessary (specifically MCL and PTCL).

In general, the 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 1 or 2) may be effectively treated with radiation alone. Although indolent NHL is responsive to radiation and chemotherapy, a continuous rate of relapse is seen in advanced stages. (1) These patients can often be re-treated, 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 (5), and median survival with conventional chemotherapy is 1 year or less. FL is the most common indolent NHL (70%–80% of cases), and often the terms indolent lymphoma and FL are used synonymously. Also included in the indolent NHL are SLL/CLL, lymphoplasmacytoid lymphoma, marginal zone lymphomas, and cutaneous T-cell lymphoma.

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

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). Prior to the development of IPI in 1993, prognosis was predominantly based on disease stage.

Based on the number of risk factors present and adjusted for patient age, the IPI defines 4 risk groups: low, low intermediate, high intermediate, and high risk, based on 5 significant risk factors prognostic of OS:

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 according to the number of adverse factors as follows: 0 or 1 is low risk, 2 is low intermediate, 3 is high intermediate, and 4 or 5 are high risk.

Patients with 2 or more risk factors have a less than 50% chance of relapse-free survival and overall survival (OS) at 5 years. Age-adjusted (aaIPI) 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 ≥ 2 , 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 a first complete remission. The proposed and validated Follicular Lymphoma International Prognostic Index (FLIPI) contains 5 adverse prognostic factors:

3. Age older than 60 years
4. Ann Arbor stage III-IV
5. Hemoglobin level less than 12.0 g/dL
6. More than 4 lymph node areas involved
7. Elevated serum lactate dehydrogenase (LDH) level

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

Mantle Cell Lymphoma (MCL)

Mantle cell lymphoma (MCL) comprises approximately 6%–8% of NHL, and has been recognized within the past 15 years 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. (8) The number of therapeutic trials are not as numerous for MCL as for other NHL as it was not widely recognized until the REAL classification. MCL shows a strong predilection for elderly men, and the majority of cases (70%) present with disseminated (stage 4) disease and extranodal involvement is common. Localized MCL is quite rare. MCL has a median survival of approximately 2–4 years, and although most patients achieve remission with first-line therapy, relapse inevitably occurs, often within 12–18 months. (9) MCL is rarely, if ever, cured with conventional therapy, and no standardized therapeutic approach to MCL is used.

There had been no generally established prognostic index for patients with MCL. Application of the IPI or FLIPI system to patients with MCL showed serious limitations (10), which included no separation of some important risk groups. In addition, some of the individual IPI and FLIPI 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.

MCL international prognostic index (MIPI):

3. Age
4. ECOG performance status
5. Serum LDH (calculated as a ratio of LDH to a laboratory's upper limit of normal)
6. White blood cell count (WBC)
 - Zero points each are assigned for age younger than 50 years, ECOG performance 0–1, LDH ratio less than 0.67, WBC less than 6,700
 - One point each for age 50–59 years, LDH ratio 0.67–0.99, WBC 6,700–9,999.
 - Two points each for age 60–69 years, ECOG 2–4, LDH ratio 1.00–1.49, WBC 10,000–14,999
 - Three points each for age 70 years or older, LDH ratio 1.5 or greater, WBC 15,000 or more

MIPI allows separation of 3 groups with significantly different prognoses: (10)

- 0–3 points=low risk, 44% of patients, median OS not reached and a 5-year OS rate of 60%
- 4–5 points=intermediate risk, 35% of patients, median OS 51 months
- 6–11 points=high risk, 21% of patients, median OS 29 months

Peripheral T-Cell Lymphoma (PTCL)

Immature T-cell lymphomas are generally treated on leukemia protocols, whereas mature (peripheral) T-cell lymphomas are usually treated with chemotherapy regimens similar to those used in DLBCL.

PTCLs are less responsive to standard chemotherapy than DLBCLs and therefore carry a worse prognosis. The poor results with conventional chemotherapy have prompted exploration of the role of HDC/SCT as first-line consolidation therapy.

Staging

The Ann Arbor staging classification is commonly used for the staging of lymphomas and is the scheme defined in the AJCC Manual for Staging Cancer. Originally developed for Hodgkin's disease, this staging scheme was later expanded to include non-Hodgkin's lymphoma.

Staging of Lymphoma: Ann Arbor Classification

Stage I

Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE)

Stage II

Involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or localized involvement of extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (IIE).

Stage 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)

Stage IV

Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement.

When services are covered for both commercial products and for Medicare HMO Blue, Medicare PPO Blue and Blue Medicare PFFS PlusRx products

We cover hematopoietic stem cell transplantation for patients with non-Hodgkin's lymphoma (NHL) subtypes considered aggressive, either allogeneic stem-cell transplant (SCT) using a myeloablative conditioning regimen or autologous SCT:

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

For patients with NHL subtypes considered indolent, either allogeneic SCT using a myeloablative conditioning regimen or autologous SCT 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.
- For patients with mantle cell lymphoma, autologous SCT

Reduced-intensity conditioning allogeneic SCT as a treatment of NHL in patients who meet criteria above for an allogeneic SCT but who do not qualify for a myeloablative allogeneic SCT

When services are not covered for both commercial products or for Medicare HMO Blue, Medicare PPO Blue and Blue Medicare PFFS PlusRx products

We do not cover either autologous SCT or allogeneic SCT:

- 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 subtypes; and.

- for peripheral T-cell lymphoma at any stage of disease.
- Tandem transplants as to treat patients with any stage, grade, or subtype of NHL.
- Allogeneic SCT to treat NHL that progresses or relapses relatively soon after a prior course of high-dose chemotherapy with *autologous* SCT.

Note:

- This policy statement is based on a strict evidence-based analysis on outcomes of allo-transplants after a failed auto-transplant.
- Harvesting of tissue for storage purposes **only** is not eligible for coverage.

Individual consideration

All our medical policies are written for the majority of people with a given condition. Each policy is based on medical science. For many of our medical policies, each individual’s unique clinical circumstances may be considered in light of current scientific literature. For consideration of an individual patient, physicians may send relevant clinical information to:

| For services already billed | Prior to performance of service |
|------------------------------------|--|
|------------------------------------|--|

| | |
|--|---|
| Blue Cross Blue Shield of Massachusetts Provider Appeals PO Box 986065 Boston, MA 02298 | Blue Cross Blue Shield of Massachusetts Case Creation/Medical Policy One Enterprise Drive Quincy, MA 02171 Tel: 1-800-327-6716 Fax: 1-888-641-5330 |
|--|---|

Managed care guidelines

Authorizations are required.

Indemnity and PPO guidelines

Authorizations are required

Other information

Reduced-intensity conditioning (RIC) would be considered an option in patients who meet criteria for an allogeneic stem-cell transplant (SCT) 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 hematopoietic SCT on the basis of overall health and disease status, allogeneic SCT using either myeloablative or RIC may be considered. However, a myeloablative conditioning regimen with allogeneic SCT may benefit younger patients with good performance status and minimal comorbidities more than allogeneic SCT with RIC.

The term salvage therapy describes chemotherapy given to patients who have either 1) failed to achieve complete remission after initial treatment for newly diagnosed lymphoma, or 2) relapsed after an initial complete remission.

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 stem 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.

Few NHL patients are considered eligible for allotransplant relatively soon after a failed autotransplant. Thus, it is unlikely that prospective trials will ever be conducted to rigorously compare outcomes of this strategy with alternatives. Nevertheless, retrospective studies (summarized below under Rationale/Sources) report long-term disease-free survival for a minority of patients treated this way. Plans that pre-authorize hematopoietic SCT may wish to consider implementing expedited external review for the rare cases when clinicians seek to treat patients with an allotransplant relatively soon after a failed autotransplant. External review may be particularly useful to evaluate the likelihood that benefit may exceed harm for a specific patient. Note that a second transplant (autologous or allogeneic) may be considered to manage relapsed NHL, if the initial autotransplant was followed by a long disease-free interval.

Clinical trials for Cancer Mandate ²

As required by law, we provide coverage for services and supplies received as part of a qualified clinical trial (for treatment of cancer) when the member is enrolled in that trial. This coverage is provided for services and supplies that are consistent with the study protocol and with the standard of care for someone with the patients' diagnosis, and that would be covered if the patient did not participate in the trials. This coverage may also be provided for investigational drugs and devices that have been approved for use as part of the trial. Coverage for services and supplies that are received as part of a qualified clinical trial is provided to the same extent as it would have been provided if the patient did not participate in the trial.

However, no coverage is provided for:

- Investigational drugs and devices that have not been approved for use in the trial.
- Investigational drugs and devices that are paid for by the manufacturer, distributor or provider of the drug or device, whether or not the drug or device has been approved for use in the trial.
- Non-covered services under the member's contract.
- Costs associated with managing the research for the trial.
- Items, services or costs that are reimbursed or otherwise furnished by the sponsor of the trial.
- Costs of services that are inconsistent with widely accepted and established national and regional standards of care.
- Costs of clinical trials that are not "qualified trials."

Guidelines for use of bone marrow

- We cover stem cells when harvested from the patient's bone marrow prior to marrow ablative therapy or from a donor's marrow after verifying the donor and recipient are well matched with respect to human leukocyte antigens (HLA). Verification of well matched HLA donor and recipient is based on the attending or treating physician's clinical judgment.

Guidelines for use of umbilical cord blood

According to the subscriber certificate, benefits are provided for covered transplant services only when they are furnished to a recipient who is an enrolled member. However, benefits will be provided for the harvesting of the donor's organ (or stem cells) when the donor is a not member as long as the recipient is a member. "Harvesting" includes the surgical removal of the donor's organ (or stem cells) and related medically necessary services and/or tests that are required to perform the transplant itself.

We cover **umbilical cord stem cell support** as an acceptable cell source for transplants that are otherwise covered for either high-dose chemo with stem cell support, or for bone marrow transplant, when all the following are met:

1. Recipient is a child or adult

2. There is no other available stem-cell donor with the same or better matching characteristics
3. Donors may be related or unrelated.

We cover collection and storage of cord blood from neonate when an allogeneic transplant is “imminent” in an identified recipient with a diagnosis that is consistent with the possible need for allogeneic transplant.

Exclusions:

1. Facility providing umbilical cord blood that is not in compliance with any existing FDA regulations governing umbilical cord transplants. FDA regulations are currently under development
2. There is a suitable stem cell donor of equal or superior HLA match¹⁵
3. Storage for future use, in case of a future need for transplant (prophylactic collection and storage).

Coding information

Procedure codes are from current CPT, HCPCS Level II, Revenue Code, and/or ICD-9-CM manuals, as recommended by the American Medical Association, Centers for Medicare and Medicaid Services and American Hospital Associations. Blue Cross Blue Shield Association national codes may be developed when appropriate.

The following codes are included below for informational purposes. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

CPT codes:

- **38206:** Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, autologous
- **38230:** Bone marrow harvesting for transplantation
- **38240:** Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic
- **38241:** Bone marrow or blood-derived peripheral stem-cell transplantation; autologous

HCPCS Codes:

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

Facility coding

ICD-9 CM procedure codes:

- **41.01:** Autologous bone marrow transplant without purging
- **41.06:** Cord blood stem-cell transplant

Policy update history

7/09, Policy created based on BCBSA medical policy #8.01.20. The portions referencing stem cell transplantation for the treatment of Non-Hodgkin lymphomas were removed from BCBSMA medical policies #126, Autologous Stem Cell Transplants and #092, Allogeneic Stem Cell Transplants.

References

References for footnote¹:

1. Physician Data Query (PDQ®). Adult non-Hodgkin lymphoma treatment. Modified 03/03/2008. Available online at <http://www.cancer.gov/cancertopics/pdq/treatment/adult-non-hodgkins/healthprofessional> . Last accessed May 2008.
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* 1994; 84(5):1361-92.
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.
4. Non-Hodgkin's Lymphomas. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. v.3.2008; Available online at http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf. Last accessed May 2008.
5. Laport GG. The role of hematopoietic cell transplantation for follicular non-Hodgkin's lymphoma. *Biol Blood Marrow Transplant* 2006; 12:59-65.
6. The International Non-Hodgkin's Lymphoma Prognostic Factors Project: A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med* 1993; 329:987-94.
7. Solal-Celigny P, Roy P, Colombat P et al. Follicular lymphoma international prognostic index. *Blood* 2004; 104(5):1258-65.
8. 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.
9. Hoster E, Dreyling M, Klapper W et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. *Blood* 2008; 111:558-65.
10. Kasamon YL. Blood or marrow transplantation for mantle cell lymphoma. *Curr Opin Oncol* 2007; 19:128-35.
11. 1987 TEC Evaluations, p. 61.
12. 1990 TEC Evaluations, p. 178.
13. 1995 TEC Assessments; Tab 28.
14. 2000 TEC Assessments; Tab 9.
15. 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.
16. 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; 108:2540-44.
17. 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.
18. 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.
19. 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; 21:3918-27.
20. 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.
21. Sweetenham JW, Santini G, Qian W et al. High-dose therapy and autologous stem-cell transplantation versus conventional-dose consolidation/maintenance therapy as postremission 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.
22. 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.
 23. 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.
 24. 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.
 25. 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.
 26. 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.
 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(2-3):198-212.
 28. 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.
 29. 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.
 30. 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*. 2008 Jan 23;(1):CD004024.
 31. 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.
 32. 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.
 33. 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.
 34. 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 Sep;36(6):491-7.
 35. 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.
 36. 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.
 37. Khouri IF, Lee MS, Romaguera J et al. Allogeneic hematopoietic transplantation for mantle-cell lymphoma: molecular remissions and evidence of graft-versus-malignancy. *Ann Oncol* 1999;10:1293-99.
 38. Villanueva ML, Vose JM. The role of hematopoietic stem cell transplantation in non-Hodgkin lymphoma. *Clin Adv Hematol Oncol* 2006; 4(7):521-30.
 39. Armitage JO. Allogeneic transplants for mantle cell lymphoma. *Ann Oncol* 2002; 13(suppl 2):9a.
 40. Vandenberghe E, Ruiz de Elvira C, Isaacson P et al. Does transplantation improve outcome in mantle cell lymphoma (MCL)? a study from the EBMT. *Blood* 2000; 96:482a.

41. Khouri IF, Lee MS, Saliba RM et al. Nonablative allogeneic stem-cell transplantation for advanced/recurrent mantle-cell lymphoma. *J Clin Oncol* 2003; 21:4407-12.
42. 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; 104:3535-42.
43. 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.
44. Geisler CH, Kolstad A, Laurell A et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. *Blood* 2008; 112(7):2687-93.
45. Evens AM, Winter JN, Hou N et al. A phase II clinical trial of intensive chemotherapy followed by consolidative stem cell transplant: long-term follow-up in newly diagnosed mantle cell lymphoma. *Br J Haematol* 2008; 140(4):385-93.
46. 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.

This document is designed for informational purposes only and is not an authorization, or an explanation of benefits, or a contract. Receipt of benefits is subject to satisfaction of all terms and conditions of the coverage. Medical technology is constantly changing, and we reserve the right to review and update our policies periodically.

©2009 Blue Cross and Blue Shield of Massachusetts, Inc. All rights reserved. Blue Cross and Blue Shield of Massachusetts, Inc. is an Independent Licensee of the Blue Cross and Blue Shield Association.

¹ Based on BCBSA policy # 8.01.20, Hematopoietic Stem Cell Transplantation for Non-Hodgkin Lymphomas

² Based on MGL - Chapter 118G, Section 1