Protocol

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

(80120)

Medical Benefit		**Effective Date**: 04/01/13	**Next Review Date**: 05/21
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, 05/19, 05/20	

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: • With indolent B-cell non-Hodgkin lymphomas	Interventions of interest are: • Autologous hematopoietic cell transplantation as first line therapy	Comparators of interest are: • Standard care	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Morbid events • Treatment-related mortality • Treatment-related morbidity
Individuals: • With aggressive B-cell non-Hodgkin lymph-omas, excluding mantle cell lymphoma	Interventions of interest are: • Autologous hematopoietic cell transplantation as consolidation therapy after first complete remission	Comparators of interest are: • Standard care	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Morbid events • Treatment-related mortality • Treatment-related morbidity
Individuals: • With non-Hodgkin lymphomas, excluding mantle cell lymphoma	Interventions of interest are: • Tandem autologous and allogeneic hematopoietic cell transplantation	Comparators of interest are: • Standard care	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Morbid events • Treatment-related mortality • Treatment-related morbidity
Individuals: • With mantle cell lymphoma	Interventions of interest are: • Autologous, allogeneic, or tandem hematopoietic cell transplantation	Comparators of interest are: • Standard care	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Morbid events • Treatment-related mortality • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With peripheral T-cell lymphoma	Interventions of interest are: • Autologous or allogeneic hematopoietic cell transplantation	Comparators of interest are: • Standard care	Relevant outcomes include: • 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 [allo-HCT]). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although umbilical cord blood is an allogeneic source, the stem cells in it are antigenically "naive" and thus are associated with a lower incidence of rejection or graft-versus-host disease. Umbilical cord blood is discussed in greater detail in 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. The relevant outcomes are overall survival (OS), disease-specific survival (DSS), 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. Observational studies have shown similar results. 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. The relevant outcomes are OS, DSS, 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 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 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 and allo-HCT, the evidence includes several nonrandomized trials. Relevant outcomes are OS, DSS, 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 MCL who receive autologous, allogeneic, or tandem HCT, the evidence includes case series. The relevant outcomes are OS, DSS, 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 receives autologous or allo-HCT, the evidence includes prospective trials and case reports. The relevant outcomes are OS, DSS, 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 two 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 allo-HCT in the first-line setting is 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 (with 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/Waldenström 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

TREATMENT FOR NON-HODGKIN LYMPHOMA

Hematopoietic Cell Transplantation

HCT is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune function in cancer patients who receive bone marrow-toxic doses of cytotoxic drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT [allo-HCT]). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Cord blood transplantation is discussed in detail in the Placental and Umbilical Cord Blood as a Source of Stem Cells Protocol.

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

CONDITIONING FOR HEMATOPOIETIC CELL TRANSPLANTATION

Conventional Conditioning

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

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

REDUCED-INTENSITY CONDITIONING ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

RIC refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. RIC regimens range from nearly total myeloablative to minimally myeloablative with lympho-ablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. In this review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative.

REGULATORY STATUS

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

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 and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services 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.

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