Protocol

Hematopoietic Stem Cell Transplantation for Hodgkin Lymphoma

(80129)

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

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 Hodgkin lymphoma	Interventions of interest are: • Autologous hematopoietic stem 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 Hodgkin lymphoma	Interventions of interest are: • Allogeneic hematopoietic stem 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 Hodgkin lymphoma	Interventions of interest are: • Tandem (autologous-autologous) stem 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 stem cell transplantation (HSCT) 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 anticancer drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates.

Summary of Evidence

The evidence for autologous HSCT in individuals who have Hodgkin lymphoma includes randomized controlled trials (RCTs), nonrandomized comparative studies, and case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. RCTs of autologous HSCT as first-line treatment have reported that autologous HSCT does not have additional benefit compared to conventional chemotherapy. Two RCTs in patients with relapsed or refractory disease have reported a benefit in progression-free survival and a trend toward a benefit in overall survival. For patients with relapsed disease after first autologous HSCT, the evidence consists of small case series and no conclusions on efficacy can be drawn. This evidence permits the conclusion that treatment of relapsed or refractory Hodgkin lymphoma with autologous HSCT improves outcomes.

The evidence for allogeneic HSCT in individuals who have Hodgkin lymphoma consists of case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. The case series report response rates for patients with refractory disease that are higher than expected with standard care. However, no definitive conclusions on the efficacy of allogeneic HSCT can be made due to the poor quality of the evidence base, and the impact on health outcomes is uncertain.

The evidence for tandem autologous HSCT in individuals who have Hodgkin lymphoma includes nonrandomized comparative studies and case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. One prospective, nonrandomized study reported that, in patients with poor prognostic markers, response to tandem autologous HSCT may be higher than that for single autologous HSCT. This study is not definitive due to the possibility of selection bias, and RCTs are needed to determine the impact of tandem autologous HSCT on outcomes.

Policy

Autologous or myeloablative allogeneic hematopoietic stem-cell transplantation (HSCT) may be considered **medically necessary** in patients with primary refractory or relapsed Hodgkin lymphoma (HL).

Tandem autologous HSCT may be considered **medically necessary**:

- in patients with primary refractory HL or
- in patients with relapsed disease with poor risk features who do not attain a complete remission to cytoreductive chemotherapy prior to transplantation (see Policy Guidelines).

Reduced-intensity allogeneic HSCT may be considered **medically necessary** to treat HL in patients:

- who have failed a prior autologous HSCT used to treat primary refractory or relapsed disease or
- in patients who would otherwise qualify for a myeloablative allogeneic transplant, but would be unable to tolerate a standard myeloablative conditioning regimen (see Policy Guidelines) or
- when insufficient stem cells are collected for an autologous HSCT.

Second autologous HSCT for relapsed lymphoma after a prior autologous HSCT is considered **investigational**.

Other uses of HSCT in patients with HL are considered **investigational**, including, but not limited to, initial therapy for newly diagnosed disease to consolidate a first complete remission.

Policy Guidelines

In the Morschhauser et al study (2008) of risk-adapted salvage treatment with single or tandem autologous

HSCT for first relapse or refractory HL,[1] poor-risk relapsed HL was defined as two or more of the following risk factors at first relapse: time to relapse less than 12 months, stage III or IV at relapse, and relapse within previously irradiated sites. Primary refractory disease was defined as disease regression less than 50% after four to six cycles of doxorubicin-containing chemotherapy or disease progression during induction or within 90 days after the end of first-line treatment.

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for RIC allogeneic HSCT. These include those with malignancies that are effectively treated with myeloablative allogeneic transplantation, but whose age (typically older than 55 or 60 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status score) preclude use of a standard myeloablative conditioning regimen.

The ideal allogeneic donors are human leukocyte antigen (HLA)–identical matched siblings. Related donors mismatched at one locus are also considered suitable donors. A matched, unrelated donor identified through the National Marrow Donor Program is typically the next option considered. Recently, there has been interest in haploidentical donors, typically a parent or a child of the patient, with whom usually there is sharing of only three of the six major histocompatibility antigens. Most patients will have such a donor; however, the risk of graft-versus-host disease and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

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.

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

Hematopoietic Stem Cell Transplantation

HSCT 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 radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT [allo-HSCT]). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although 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 (GVHD). Cord blood is discussed in greater 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 HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome with allo-HSCT. Compatibility is established by typing of HLA using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR (antigen-D related) 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 (with the exception of umbilical cord blood).

Conventional Preparative Conditioning for HSCT

The conventional ("classical") practice of allo-HSCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hemato-

poietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self-immunologic effector cells that develop after engraftment of allogeneic stem cells within the patient's bone marrow space. While the slower GVM effect is considered to be 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 sufficiently fit medically to tolerate substantial adverse effects that include preengraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allo-HSCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increase susceptibility of the patient to opportunistic infections.

The success of autologous HSCT is predicated on the ability of cytotoxic chemotherapy with or without radiation 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 HSCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

Reduced-Intensity Conditioning for Allo-HSCT

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden but also to minimize as much as possible associated treatment-related morbidity and nonrelapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HSCT 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, the term RIC will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

Hodgkin Lymphoma

Hodgkin lymphoma is a relatively uncommon B-cell lymphoma. In 2011, the estimated number of cases in the United States was approximately 8830 new diagnoses and 1300 deaths.[2] The disease has a bimodal distribution, with most patients diagnosed between the ages of 15 and 30 years, with a second peak in adults aged 55 years and older.

The 2008 World Health Organization classification divides Hodgkin lymphoma into two main types[3]:

1. "Classical" Hodgkin lymphoma (CHL)
    - Nodular sclerosis
    - Mixed cellularity
    - Lymphocyte depleted
    - Lymphocyte rich
2. Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)

In Western countries, CHL accounts for 95% of cases of Hodgkin lymphoma, and for NLPHL, only 5%.[4] Classic Hodgkin lymphoma is characterized by the presence of neoplastic Reed-Sternberg cells in a background of numerous non-neoplastic inflammatory cells. NLPHL lacks Reed-Sternberg cells but is characterized by the presence of lymphocytic and histiocytic cells termed "popcorn cells."[4]

The following staging system for Hodgkin lymphoma recognizes that the disease is thought to typically arise in a single lymph node and spread to contiguous lymph nodes with eventual involvement of extranodal sites. The staging system attempts to distinguish patients with localized Hodgkin lymphoma who can be treated with extended field radiation from those who require systemic chemotherapy.

Staging for Hodgkin Lymphoma

Staging for Hodgkin lymphoma is based on the Ann Arbor staging system. Each stage is subdivided into A and B categories. "A" indicates no systemic symptoms are present and "B" indicates the presence of systemic symptoms, which include unexplained weight loss of more than 10% of body weight, unexplained fevers, or drenching night sweats.[4]

Stage I - Involvement of a single lymph node region (I) or localized involvement of a single extralymphatic organ or site (IE).

Stage II - Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single associated extralymphatic organ or site and its regional lymph node(s) with or without involvement of other lymph node regions on the same side of the diaphragm (IIE). The number of lymph node regions involved should be indicated by a subscript (e.g., II_2).

Stage III - Involvement of lymph node regions or structures on both sides of the diaphragm. These patients are further subdivided as follows:

III-1: disease limited to spleen or upper abdomen

III-2: periaortic or pelvic node involvement

Stage IV - Disseminated (multifocal) involvement of one or more extralymphatic organs, with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement.

Patients with Hodgkin lymphoma are generally classified into three groups: early-stage favorable (stage I-II with no B symptoms or large mediastinal lymphadenopathy), early-stage unfavorable (stage I-II with large mediastinal mass, with or without B symptoms; stage IB-IIB with bulky disease), and advanced-stage disease (stage III-IV).[4]

Patients with nonbulky stage IA or IIA disease are considered to have clinical early-stage disease. These patients are candidates for chemotherapy, combined modality therapy, or radiotherapy alone.[2] Patients with obvious stage III or IV disease, bulky disease (defined as a 10-cm mass or mediastinal disease with a transverse diameter exceeding 33% of the transthoracic diameter), or the presence of B symptoms will require combination chemotherapy with or without additional radiotherapy.[2]

Hodgkin lymphoma is highly responsive to conventional chemotherapy, and up to 80% of newly diagnosed patients can be cured with combination chemotherapy and/or radiotherapy. Patients who prove refractory or who relapse after first-line therapy have a significantly worse prognosis. Primary refractory Hodgkin lymphoma is defined as disease regression of less than 50% after four to six cycles of anthracycline-containing chemotherapy, disease progression during induction therapy, or progression within 90 days after the completion of first-line treatment.[5]

In patients with relapse, the results of salvage therapy vary depending on a number of prognostic factors, as follows: the length of the initial remission, stage at recurrence, and the severity of anemia at the time of relapse.[6] Early and late relapse are defined as less or more than 12 months from the time of remission, respec-

tively. Approximately 70% of patients with late first relapse can be salvaged by autologous HSCT but not more than 40% with early first relapse.[7]

Only approximately 25% to 35% of patients with primary progressive or poor-risk recurrent Hodgkin lymphoma achieve durable remission after autologous HSCT, with most failures being due to disease progression after transplant. Most relapses after transplant occur within one to two years, and once relapse occurs posttransplant, median survival is less than 12 months.

Regulatory Status

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

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.

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