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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 Hodgkin lymphoma 	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 of 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 relapsed or refractory Hodgkin lymphoma 	Interventions of interest are: <ul style="list-style-type: none"> • Autologous hematopoietic cell transplantation 	Comparators of interest are: <ul style="list-style-type: none"> • Standard of 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 relapsed Hodgkin lymphoma after an autologous hematopoietic cell transplantation 	Interventions of interest are: <ul style="list-style-type: none"> • Second autologous hematopoietic cell transplantation 	Comparators of interest are: <ul style="list-style-type: none"> • Standard of 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 Hodgkin lymphoma 	Interventions of interest are: <ul style="list-style-type: none"> • Allogeneic hematopoietic cell transplantation as first-line therapy 	Comparators of interest are: <ul style="list-style-type: none"> • Standard of 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: • With relapsed or refractory Hodgkin lymphoma	Interventions of interest are: • Allogeneic hematopoietic cell transplantation	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Morbid events • Treatment-related mortality • Treatment-related morbidity
Individuals: • With relapsed Hodgkin lymphoma after an autologous hematopoietic cell transplantation	Interventions of interest are: • Allogeneic hematopoietic cell transplantation	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Morbid events • Treatment-related mortality • Treatment-related morbidity
Individuals: • With relapsed or refractory Hodgkin lymphoma	Interventions of interest are: • Reduced-intensity conditioning with allogeneic hematopoietic cell transplantation	Comparators of interest are: • Standard of 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 hematopoietic cell transplantation	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Morbid events • Treatment-related mortality • Treatment-related morbidity

DESCRIPTION

Hodgkin lymphoma (HL) results from a clonal expansion of a B-cell lineage, characterized by the presence of Reed-Sternberg cells on pathology. Standard treatment is based on the stage at presentation and may involve chemotherapy with or without radiotherapy. Hematopoietic cell transplantation (HCT) has been used for HL, particularly in the setting of relapse or refractory disease.

SUMMARY OF EVIDENCE

AUTOLOGOUS HCT

For individuals who have HL who receive autologous HCT as first-line therapy, the evidence includes randomized controlled trials (RCTs). The relevant outcomes are overall survival (OS), disease-specific survival (DSS), change in disease status, morbid events, and treatment-related mortality (TRM) and morbidity. RCTs of autologous HCT as first-line treatment have reported that this therapy does not provide additional benefit compared with conventional chemotherapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have relapsed or refractory HL who receive autologous HCT, the evidence includes RCTs, a meta-analysis, nonrandomized comparative studies, and case series. The relevant outcomes are OS, DSS, change in disease status, morbid events, and TRM. Two RCTs in patients with relapsed or refractory disease have

reported a benefit in progression-free survival and a trend toward a benefit in OS. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have relapsed HL after an autologous HCT who receive a second autologous HCT, the evidence includes case series. The relevant outcomes are OS, DSS, change in disease status, morbid events, TRM and morbidity. No RCTs or nonrandomized comparative studies were identified. In a case series, TRM at 100 days was 11%; at a median follow-up of 72 months, the mortality rate was 73%. The evidence is insufficient to determine the effects of the technology on health outcomes.

ALLOGENEIC HCT

For individuals who have HL who receive allo-HCT as first-line therapy, the evidence includes no published studies. The relevant outcomes are OS, DSS, change in disease status, morbid events, TRM and morbidity. No studies specifically addressing allo-HCT as first-line treatment for HL were identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have relapsed or refractory HL who receive allo-HCT, the evidence includes a number of case series and a meta-analysis. The relevant outcomes are OS, DSS, change in disease status, morbid events, TRM and morbidity. A 2016 meta-analysis identified 38 case series evaluating allo-HCT for relapsed or refractory HL. The pooled analysis found a six-month OS rate of 83% and a three-year overall survival rate of 50%. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have relapsed HL after autologous HCT who receive allo-HCT, the evidence includes case series and a meta-analysis. The relevant outcomes are OS, DSS, change in disease status, morbid events, TRM and morbidity. A 2016 meta-analysis of 38 case series found that a previous autologous HCT followed by allo-HCT was significantly associated with higher one- and two-year OS rates and significantly higher recurrence-free survival rates at one year compared with no previous autologous HCT. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have relapsed or refractory HL who receive reduced-intensity conditioning with allo-HCT, the evidence includes case series, cohort studies, and a systematic review. The relevant outcomes are OS, DSS, change in disease status, morbid events, TRM and morbidity. A 2015 systematic review cited a number of studies, including some with comparison groups, showing acceptable outcomes after reduced-intensity conditioning with allo-HCT in patients with relapsed or refractory HL. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

TANDEM AUTOLOGOUS HCT

For individuals who have HL who receive tandem autologous HCT, the evidence includes nonrandomized comparative studies and case series. The relevant outcomes are OS, DSS, change in disease status, morbid events, TRM and morbidity. One prospective, nonrandomized study reported that, in patients with poor prognostic markers, response to tandem autologous HCT might be higher than for single autologous HCT. This study was not definitive due to potential selection bias; RCTs are needed to determine the impact of tandem autologous HCT on health outcomes in this population. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

Autologous hematopoietic cell transplantation (HCT) may be considered **medically necessary** in patients with primary refractory or relapsed Hodgkin lymphoma.

Allogeneic HCT, using either myeloablative or reduced-intensity conditioning regimens, may be considered

medically necessary in patients with primary refractory or relapsed Hodgkin lymphoma.

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

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

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

Other uses of HCT in patients with Hodgkin lymphoma 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 (2008) study of risk-adapted salvage treatment with single or tandem autologous HCT for first relapse or refractory HL, 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 reduced-intensity conditioning (RIC) allo-HCT. They 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 the use of a standard myeloablative conditioning regimen.

The ideal allogeneic donors are human leukocyte antigen (HLA)–identical matched siblings. Related donors mismatched at a single 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 Medicare-approved transplant center review and decide whether the patient is an appropriate candidate for the transplant.

BACKGROUND

HODGKIN LYMPHOMA

HL is a relatively uncommon B-cell lymphoma. In 2017, the estimated number of new cases in the United States was approximately 8260 and 1070 estimated deaths.¹ 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 divided HL into two main types²; these classifications did not change in the 2016 update³:

1. “Classical” HL (CHL)
 - Nodular sclerosis
 - Mixed cellularity
 - Lymphocyte depleted
 - Lymphocyte rich
2. Nodular lymphocyte-predominant HL.

In Western countries, “Classical” HL accounts for 95% of cases of HL and, for nodular lymphocyte-predominant HL, only 5%.⁴ “Classical” HL is characterized by the presence of neoplastic Reed-Sternberg cells in a background of numerous non-neoplastic inflammatory cells. Nodular lymphocyte-predominant HL lacks Reed-Sternberg cells but is characterized by the presence of lymphocytic and histiocytic cells termed “popcorn cells”.

Staging

The Ann Arbor staging system for HL recognizes that the disease is thought typically to 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 HL who can be treated with extended field radiation from those who require systemic chemotherapy.

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 (see Table 1).⁴

Table 1. Ann Arbor Staging System for Hodgkin Lymphoma

Stage	Area of Concern
I	Single lymph node region (I) or localized involvement of a single extralymphatic organ or site (IE)
II	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).
III	Involvement of lymph node regions or structures on both sides of the diaphragm. These patients are further subdivided as follows: <ul style="list-style-type: none"> • III-1: disease limited to spleen or upper abdomen • III-2: periaortic or pelvic node involvement
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 HL 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 a large mediastinal mass, with or without B symptoms; stage IB-IIB with the bulky disease), and advanced-stage disease (stage III-IV).⁴

Treatment

Patients with nonbulky stage IA or IIA disease are considered to have the clinically early-stage disease. These patients are candidates for chemotherapy, combined modality therapy, or radiotherapy alone.^{4,5} Patients with obvious stage III or IV disease, bulky disease (defined as a 10 cm mass or mediastinal disease with a transverse diameter >33% of the transthoracic diameter), or the presence of B symptoms will require combination chemotherapy with or without additional radiotherapy.^{4,5}

HL is highly responsive to conventional chemotherapy, and up to 80% of newly diagnosed patients can be cured with chemotherapy and/or radiotherapy. Patients who prove refractory or who relapse after first-line therapy have a significantly worse prognosis. Primary refractory HL 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.⁶

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.⁷ Early and late relapse are defined as less or more than 12 months from the time of remission, respectively. Approximately 70% of patients with late first relapse can be salvaged by autologous HCT but not more than 40% with early first relapse.⁸

Only 25% to 35% of patients with primary progressive or poor-risk recurrent HL achieve durable remission after autologous HCT, 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.

Hematopoietic Cell Transplantation

HCT is a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs with or without whole body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from 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 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. Cord blood 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. However, immunologic compatibility between donor and patient is critical for achieving a good outcome with allo-HCT. Compatibility is established by typing of human leukocyte antigen (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 (except umbilical cord blood).

Conditioning for HCT

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 destroy endogenous hematopoietic 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 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 graft-versus-malignancy 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 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 allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease, which also increase susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiotherapy to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the

patient before undergoing bone marrow ablation. 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 Allo-HCT

RIC refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiotherapy 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 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 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-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 this protocol, the term RIC refers to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) 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 PROTOCOL

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

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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