Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Title: BMT - Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Description/Background

HODGKIN LYMPHOMA
Hodgkin Lymphoma (HL) is a relatively uncommon B cell lymphoma. In 2023, the estimated number of new cases in the United States was approximately 8,830 and 900 estimated deaths related to HL.(1) The disease has a bimodal distribution, with most patients diagnosed between the ages of 20 and 39 years, with a second peak in adults aged 65 years and older.

The 2008 World Health Organization (WHO) classification divides HL into two main types;(2) these classifications did not change in the 2022 update.(3)

1. "Classical" HL (CHL)
   - Nodular sclerosis
   - Mixed cellularity
   - Lymphocyte depleted
   - Lymphocyte rich
2. Nodular Lymphocyte-Predominant HL (NLPHL)

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 including unexplained weight loss of more than 10% of body weight, unexplained fevers >38° C, 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 extra lymphatic organ or site (I_E)
II	Two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single associated extra lymphatic 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 (II_E). 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, which may involve an extra lymphatic organ or site (III_E), spleen (III_S), or both (III_{E+S})
IV	Disseminated (multifocal) involvement of one or more extra lymphatic organs, with or without associated lymph node involvement, or isolated extra lymphatic organ involvement with distant (nonregional) nodal involvement

Patients with HL are generally classified into 3 groups: early-stage favorable (stage I–II with no B symptoms, large mediastinal lymphadenopathy), or other unfavorable factors), early-stage unfavorable (stage I-II with a large mediastinal mass, multiple involved nodal regions, B symptoms, extranodal involvement, or elevated erythrocyte sedimentation rate ≥50) , and advanced-stage disease (stage III-IV).(4)

Treatment

Patients with non-bulky 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.(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.

HL 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 HL is defined as disease regression of less than 50% after 4–6 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 upon 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 1–2 years, and once relapse occurs post-transplant, median survival is less than 12 months.

Hematopoietic Cell Transplantation
HCT is a procedure in which hematopoietic cells are intravenously infused to restore bone marrow function and immune 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 donor (allogeneic HCT [allo-HCT]). These cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allogenic 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 HCT

Myeloablative (Conventional) Conditioning
The myeloablative (conventional) practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation. Intense conditioning regimens are limited to individuals whose health status is sufficient to tolerate the administration of cytotoxic agents with 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 initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self-immunologic effector cells. While the slower GVM effect is considered the potentially curative component, it may be overwhelmed by substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the 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 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 with presumably normal hematopoietic stem cells obtained from the individual before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the individual's disease is in complete remission. Individuals who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

Reduced-Intensity or Non-myeloablative Conditioning for Allo-HCT
Reduced-intensity conditioning (RIC), sometimes referred to as non-myeloablative (NMA) conditioning, refers to the pretransplant use of lower doses of cytotoxic drugs with or without less intense regimens of radiotherapy than are used in myeloablative conditioning treatments. Although the definition of RIC/NMA 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/NMA 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. These RIC/NMA regimens range from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and individual condition. Individuals who undergo RIC/NMA with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism.

Targeted Chemotherapy and Autologous HCT for the Treatment of Hodgkin Lymphoma
A recent important development in the HL treatment landscape is the emergence of several novel agents that are now being used as alternatives to stem cell transplantation in patients at high-risk for relapse after chemotherapy or relapse following autologous HCT. These agents include brentuximab vedotin, a CD30-directed antibody-drug conjugate, and nivolumab and pembrolizumab which are 2 programmed death receptor-1 (PD-1) blocking antibodies. The U.S. Food and Drug Administration (FDA) regulatory status of these agents for the treatment of Hodgkin lymphoma is summarized in Table 2.

Brentuximab vedotin was evaluated in a large, phase 3, multinational, double-blind randomized controlled trial known as the AETHERA trial (abbreviation definition unknown). Moskowitz et al (2015),(9) reported on the outcomes for 329 individuals with HL with risk factors for post-transplantation relapse or progression (e.g., primary refractory HL, relapse <12 months after initial therapy, and/or relapse with extranodal disease). Results showed that early consolidation with brentuximab vedotin after autologous HCT significantly improved 2-year progression-free survival (PFS) versus placebo (63% versus 51%, hazard ratio [HR] 0.57; 95% confidence interval [CI], 0.40-0.81). At 5-year follow-up, the significant PFS benefit for brentuximab vedotin persisted (59% versus 41%; HR 0.52; 95% CI, 0.38 to 0.72).(10) In addition, a study by Smith et al (2018)(1) of tandem autologous HCT observed that the 2-year PFS of 63% for brentuximab vedotin demonstrated in the AETHERA RCT "matches" the 2-year PFS rates for tandem autologous HCT.

A survival benefit with novel agents has been found in the setting of relapse post-autologous HCT. Bair et al (2017) reported a retrospective comparative analysis that evaluated the outcomes of 87 individuals with relapsed/refractory HL who had relapsed post-autologous HCT.(12) Compared to individuals who did not receive any novel agents, those that received novel agents, including brentuximab vedotin or nivolumab, experienced a significant improvement in median overall survival (85.6 versus 17.1 months; P<.001). The availability of safe and effective targeted systemic therapy represents an alternative to the use of a second autologous transplant or planned tandem autologous HCT for HL consolidation treatment or relapse/refractory disease treatment.

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.

Table 2 describes several novel agents that have been approved by the U.S. FDA for use as alternatives to tandem autologous HCT or a second autologous HCT in individuals at high-risk for, or with, respectively, refractory or relapsed HL following autologous HCT.

Table 2. Novel Agents Approved by the U.S. Food and Drug Administration (FDA)

Drug	BLA	Type of Agent	Manufacturer	FDA-approved indications for post-autologous HCT use	Date FDA approved
Brentuximab vedotin	125388	CD30-directed antibody-drug conjugate	Seattle Genetics	Classical HL at high risk of relapse or progression as post-autologous HCT consolidation Classical HL after failure of autologous HCT	Aug 2015
Nivolumab	125554	Programmed death receptor-1 (PD-1) blocking antibody	Bristol Myers Squibb	Classical HL that has relapsed or progressed after autologous HCT and post-transplantation brentuximab vedotin	May 2016
Pembrolizumab	125514	Programmed death receptor-1 (PD-1) blocking antibody	Merck Sharp Dohme	Adult and pediatric patients with refractory classical HL, or who have relapsed after 3 or more prior lines of therapy[a]	Mar 2017

BLA: Biologic License Application; FDA: U.S. Food and Drug Administration; HL: Hodgkin Lymphoma; HCT: Hematopoietic Cell Transplantation

[a]In the pivotal multicenter, nonrandomized, open-label study, prior lines of therapy included prior autologous HCT (61%) and brentuximab (83%)

Medical Policy Statement

The safety and effectiveness of autologous or myeloablative allogeneic hematopoietic cell transplantation (HCT) and reduced-intensity allogeneic HCT have been established. They can be useful therapeutic options for individuals with primary refractory or relapsed Hodgkin lymphoma (HL) who meet specific criteria.

Other uses for HCT are experimental/investigational.

Inclusionary and Exclusionary Guidelines

Inclusions:

Autologous HCT:

- Individuals with primary refractory HL
- Individuals with relapsed HL

Allogeneic HCT, using either myeloablative or reduced intensity conditioning HCT:

- Individuals with primary refractory HL
- Individuals with relapsed HL

Exclusions:

- A second autologous cell transplant for relapsed lymphoma after a prior autologous HCT.
- Other uses of HCT in individuals with HL including, but not limited to, initial therapy for newly diagnosed disease to consolidate a first complete remission.
- Tandem autologous HCT

Policy Guidelines

In the Morschhauser et al (2008) study of risk-adapted salvage treatment with single or tandem autologous hematopoietic cell transplantation for first relapse or refractory Hodgkin lymphoma, poor-risk relapsed Hodgkin lymphoma 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. The 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 allogeneic hematopoietic cell transplantation. They include those with malignancies that are effectively treated with myeloablative allogeneic transplantation, but whose age (typically >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–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 3 of the 6 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.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

38204	38205	38206	38207	38208	38209
38210	38211	35212	38213	38214	38215
38230	38232	38240	38241	38242	38243
81265	81266	81267	81268	81370	81371
81372	81373	81374	81375	81376	81377
81378	81379	81380	81381	81382	81383
86812	86813	86816	86817	86821	S2140
S2142	S2150				

Other codes (investigational, not medically necessary, etc.):

N/A

POTENTIAL CONTRAINDICATIONS FOR TRANSPLANT:

Note: Final patient eligibility for transplant is subject to the judgment and discretion of the requesting transplant center.

The selection process for approved tissue transplants is designed to obtain the best result for each patient. Therefore, potential contraindications to HCT may include, but are not limited to:

- Poor cardiac function: Ejection fraction should be greater than 45% with no overt symptoms of congestive heart failure.
- Poor pulmonary function: Pulmonary function tests must be greater than or equal to 50% of predicted value.
- Poor renal function: Renal creatinine clearance should be greater than 40 ml/min or creatinine must be less than or equal to 2mg/dl.
- Poor liver function: There should be no history of severe chronic liver disease
- Presence of HIV or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus (HTLV-1).

Clinical documentation supplied to the health plan must demonstrate that attending staff at the transplant center have considered all contraindications as part of their overall evaluation of potential organ transplant recipient and have decided to proceed.

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, two domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Clinical Context and Therapy Purpose

The indications being reviewed in this policy are as follows:

- Autologous hematopoietic cell transplantation as first-line therapy to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with Hodgkin lymphoma.
- Autologous hematopoietic cell transplantation as a treatment option that is an alternative to or an improvement on existing therapies in individuals with relapsed or refractory Hodgkin lymphoma.
- Second autologous hematopoietic cell transplant as a treatment option that is an alternative to or an improvement on existing therapies in individuals with relapsed Hodgkin lymphoma after an autologous hematopoietic cell transplantation.
- Allogeneic hematopoietic cell transplantation as a first-line therapy treatment option that is an alternative to or an improvement on existing therapies in individuals with Hodgkin lymphoma.
- Allogeneic hematopoietic cell transplantation as a treatment option that is an alternative to or an improvement on existing therapies in individuals with relapsed or refractory Hodgkin lymphoma.
- Allogeneic hematopoietic cell transplantation as a treatment option that is an alternative to or an improvement on existing therapies in individuals with relapsed Hodgkin lymphoma after an autologous hematopoietic cell transplantation.
- Reduced-intensity conditioning with allogeneic hematopoietic cell transplantation as a treatment option that is an alternative to or an improvement on existing therapies in individuals with relapsed or refractory Hodgkin lymphoma.
- Autologous hematopoietic cell transplantation as a treatment option that is an alternative to or an improvement on existing therapies in individuals with Hodgkin lymphoma.

Populations
The relevant population of interest are individuals with a diagnosis of the indication being reviewed.

Interventions
The therapy being considered is autologous or allogeneic hematopoietic cell transplantation used according to the indication being reviewed.

Comparators
Comparators of interest include standard of care.

Outcomes
The general outcomes of interest are overall survival, disease specific survival, change in disease status, morbid events, treatment-related mortality, and treatment-related morbidity.

Follow-up over years is of interest for relevant outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION FOR HODGKIN LYMPHOMA

First-Line Therapy for Hodgkin Lymphoma

Randomized Controlled Trials

Federico et al (2003) published results from an RCT of 163 patients with unfavorable Hodgkin lymphoma (HL) who had received autologous hematopoietic cell transplantation (HCT) or additional standard chemotherapy for consolidation after initial conventional chemotherapy.(13) Patients were randomized to high-dose chemotherapy (HDC) followed by autologous HCT (n=83) or to four additional courses of the same standard chemotherapy used in the induction phase (n=80). After treatment, complete remission (CR) was achieved in 92% of patients in the autologous HCT arm and 89% in the standard chemotherapy arm (p=0.6). Five-year survival rates (overall, failure-free, and relapse-free) did not differ between the treatment groups, and the authors concluded that HDC with autologous HCT offered no benefit in outcomes over conventional chemotherapy as first-line therapy for patients with advanced HL.

Carella et al (2009) published 10-year follow-up results for the Federico study.(14) Ten-year overall survival (OS) rates were 85% (95% confidence interval [CI], 78% to 90%) for the HDC autologous HCT group and 84% (95% CI, 77% to 89%; p=0.7) for the standard chemotherapy group. Ten-year failure-free survival rates were 79% (95% CI, 72% to 85%) for the HDC autologous HCT group and 75% (95% CI, 67% to 82%; p=0.8) for the standard chemotherapy group. The authors concluded that, after a median follow-up of 107 months, their data suggested patients who respond to induction therapy with conventional chemotherapy do not achieve superior outcomes with consolidation with HDC and autologous HCT.

Section Summary: Autologous HCT as First-Line Therapy for Hodgkin Lymphoma

A small number of RCTs have evaluated the use of autologous HCT as first-line treatment for HL, and these trials have reported no benefit above that of conventional chemotherapy.

Relapsed or Refractory Hodgkin Lymphoma

Systemic Reviews

A systematic review and meta-analysis of available RCTs on HCT for patients with relapsed or refractory HL was published by Rancea et al in 2014.(15) Reviewers included three RCTs, 2 (1993, 2002) of which compared HDC plus autologous HCT with conventional treatment.(16,17) Both trials (described below) were judged to be at moderate risk of bias using the Cochrane criteria. Combined analysis for the outcome of OS demonstrated a hazard ratio of 0.67 for patients treated with autologous HCT, which was not statistically significant (95% CI, 0.41 to 1.07). For the outcome of progression-free survival (PFS), there was a significant improvement for autologous HCT treatment, with a hazard ratio of 0.55 (95% CI, 0.35 to 0.86).

Randomized Controlled Trials

The British National Lymphoma Investigation study (1993) was the first to show that autologous HCT offered patients with relapsed or refractory HL a PFS benefit over conventional chemotherapy.(18) Forty patients with relapsed or refractory HL were given chemotherapy without transplant (n=20) or autologous HCT after HDC (n=20).(16) A significantly better event-free survival rate at 3 years (53%) was reported for patients who underwent HCT than for those who did not (10%).

Subsequently, these findings were confirmed in a larger 2002 trial by the German Hodgkin Study Group and European Group for Blood and Marrow Transplantation.(17) Patients relapsing after initial chemotherapy were randomized to chemotherapy without transplant or to autologous HCT. In the final analysis of 144 patients, freedom from treatment failure at three years was 55% in the transplanted group vs 34% in the non-transplanted group. This benefit was maintained in a 2007 subgroup analysis, regardless of early or late relapse, and the results were confirmed in follow-up data at 7 years.(19)

Nonrandomized Studies

In addition to the RCTs, several large retrospective studies identified in a systematic review have reported event-free survival rates ranging from 25% to 60%, with OS rates from 35% to 66%, showing that disease status before autologous HCT was the most important prognostic factor for the final outcome.(6)

A retrospective observational cohort study by Merryman et al (2021) evaluated autologous HCT after anti-programmed death-1 (PD-1) therapy for patients with relapsed or refractory HL.(20) Seventy-eight patients were identified who underwent autologous HCT as a third-line (or later) treatment; 74% of patients underwent autologous HCT after anti-PD-1 treatment and 26% of patients received anti-PD-1 treatment along with additional therapy prior to autologous HCT. The 18-month PFS and OS after autologous HCT were 81% (95% CI, 69 to 89) and 96% (95% CI, 87 to 99), respectively. Favorable outcomes were reported for patients who had received greater than 4 systemic therapies before autologous HCT (18-month PFS, 73%), who were refractory to 2 consecutive therapies immediately prior to anti-PD-1 treatment (18-month PFS, 78%), and who had positive pre-HCT positron emission tomography (PET) (18-month PFS, 75%); patients who were non-responders to anti-PD-1 treatment had inferior outcomes (18-month PFS, 51%).

Section Summary: Autologous HCT for Relapsed or Refractory HL

RCTs and a meta-analysis have evaluated use of auto-HCT for relapsed or refractory HL. The studies reported no difference in OS, but a significant improvement in PFS, for patients treated with autologous HCT.

Second Autologous HCT for Relapsed HL After Prior Autologous HCT

Case Series

There is limited experience with second autologous HCT, and treatment-related mortality is high (25% to 40%).(16) Smith et al (2008) reported the outcomes of 40 patients (21 with HL and 19 with non-Hodgkin lymphoma) who underwent a second autologous HCT for relapsed lymphoma.(21) Reported results were combined for the 2 populations, but authors stated that the outcomes for both patient groups were similar. Median age at second HCT was 38 years (range, 16-61 years). In 82% of patients, the second HCT was performed more than one year

after the first. Treatment-related mortality at day 100 posttransplant was 11% (95% CI, 3% to 22%). At a median follow-up of 72 months (range, 12-124 months) after the second HCT, 73% of patients had died - 62% due to relapsed lymphoma. One-, three-, and five-year PFS estimates were 50% (95% CI, 34% to 66%), 36% (95% CI, 21% to 52%), and 30% (95% CI, 16% to 46%), respectively. Corresponding OS estimates were 65% (95% CI, 50% to 79%), 36% (95% CI, 22% to 52%), and 30% (95% CI, 17% to 46%), respectively. Study limitations included the absence of an appropriate comparison group and lack of data on how many patients were considered for a second HCT but were unable to mobilize sufficient stem cells or were otherwise unable to proceed to the second transplant. Finally, heterogeneity of the preparative regimens used in this population precluded comparison of efficacy.

Section Summary: Second Autologous HCT for Relapsed HL after Prior Autologous HCT

The evidence is limited to case series; no RCTs or nonrandomized comparative studies were identified. In one series, treatment-related mortality at 100 days was 11%, and the mortality rate was 73% at a median follow-up of 72 months.

ALLOGENEIC HCT FOR HL

First-Line Therapy for Hodgkin Lymphoma

The application of allogeneic HCT (allo-HCT) to the treatment of patients with HL appears limited, due to a high procedure-related mortality. No controlled trials evaluating allo-HCT as first-line treatment for HL were identified. In addition, 2015 and 2016 systematic reviews of HCT for HL did not discuss studies using allo-HCT as first-line therapy.(22,23)

Section Summary: Allo-HCT as First-Line Therapy for HL

No studies specifically addressing allo-HCT as first-line treatment for HL were identified.

Relapsed or Refractory Hodgkin Lymphoma

Systematic Reviews

Rashidi et al (2016) published a systematic review and meta-analysis of studies evaluating allo-HCT in HL.(23) Thirty-eight studies were selected. Three studies included more than 1 series and were divided into more than one group; a total of 42 series were included in the meta-analysis. Sample sizes of included studies ranged from 5 to 285 patients (n=1850 patients). Twenty-eight studies were retrospective and 14 prospective. None was an RCT. Median follow-up in the studies ranged from 11 to 104 months. Results of the meta-analyses are shown in Table 3.

Table 3. Meta-Analytic Outcomes

Follow-Up	Relapse-Free Survival (95% CI), %	Overall Survival (95% CI), %
6 months	77 (59 to 91)	83 (75 to 91)
1 year	50 (42 to 57)	68 (62 to 74)
2 years	37 (31 to 43)	58 (52 to 64)
3 years	31 (25 to 37)	50 (41 to 58)

Adapted from Rashidi et al (2016).
CI: confidence interval.

In multivariate analysis, more recent studies (i.e., those that started to accrue patients in 2000 or later) had significantly higher 6-month and 1-year survival rates than older studies.

Section Summary: Allo-HCT as for Relapsed or Refractory HL
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 OS rate of 50%.

Allo-HCT for Relapsed Hodgkin Lymphoma After Prior Autologous HCT
The Rashidi et al (2016) meta-analysis (described above) included 38 case series assessing patients who underwent allo-HCT after a prior failed autologous HCT.(23) In a multivariate analysis of factors associated with survival outcomes, reviewers found that a previous autologous HCT was significantly associated with higher 1-year (p=0.012) and two-year) p=0.040) OS rates and significantly higher relapse-free survival at one year (p=0.005) compared with no previous autologous HCT.

Section Summary: Allo-HCT for Relapsed HL After Prior Autologous HCT
A 2016 meta-analysis found that a previous autologous HCT was significantly associated with higher OS rates and significantly higher relapse-free survival rates compared with no previous autologous HCT.

Reduced-Intensity Conditioning With Allo-HCT

Systematic Reviews
Perales et al (2015) conducted an evidence review as part of the development of clinical guideline on HCT for HL.(22) Reviewers evaluated a number of studies that showed better outcomes with reduced-intensity conditioning (RIC) than with myeloablative conditioning regimens. For example, reviewers cited a 2008 study by the European Group for Blood and Marrow Transplantation reporting outcomes in 89 HL patients with relapsed or refractory disease who received an RIC with allo-HCT and were compared with 79 patients who received myeloablative conditioning (i.e., conventional group).(24) Sixty-two percent of the RIC group had undergone a previous autologous HCT vs 41% of the myeloablative group. Although the incidence of relapse was nearly double in the RIC group (57% vs 30%), after a median follow-up for surviving patients of 75 months (range, 12-120 months), 24 in the RIC group (26.9%) and 18 in the conventional group (22.8%) were alive. Five-year OS rates were 28% (95% CI, 18% to 38%) for the RIC group and 22% (95% CI, 13% to 31%) for the conventional group. Independent adverse prognostic factors for OS were a previously failed autologous HCT (relative risk [RR], 1.59; 95% CI, 1.07 to 2.35; p=0.02), the use of myeloablative conditioning (RR=1.62; 95% CI, 1.27 to 3.29; p=0.04), and the presence of refractory disease (RR=1.51; 95% CI, 1.03 to 2.21; p=0.003). Perales et al concluded: “As a result, the preferred conditioning intensity in adult patients with relapsed/refractory HL is RIC, which results in acceptable TRM [treatment-related mortality] including in patients who have had a prior ASCT [autologous stem cell transplant].”

Nonrandomized Study
Sureda et al (2012) published a phase II study (HDR-ALLO) of allogeneic stem cell transplantation (allo-HCT) after RIC for patients with relapsed or refractory Hodgkin’s lymphoma.(25) Ninety-two patients were included, of which 90% had received more than 2 lines of therapy, 87% prior radiotherapy, and 86% had failed a previous auto-HCT. Fourteen individuals (15%) progressed under salvage therapy and were excluded from further study treatment. The remaining 78 patients proceeded to allograft (50 were in complete or partial remission and 29 in stable disease). Non-relapse mortality was 8% at 100 days and 15% at 1

year; OS was 71% at 1 year and 43% at 4 years from trial entry. For those who received allo-HCT, PFS was 48% at one year and 24% at 4 years. The study was limited by its small sample size and by the non-relapse mortality being adversely influenced by older age, poor performance score and by the presence of refractory disease.

Section Summary: Reduced-Intensity Conditioning With Allo-HCT
A 2015 systematic review assessed a number of studies, including some with comparison groups, showing acceptable outcomes after RIC with allo-HCT in patients with relapsed or refractory HL. A phase II study found slightly improved results for patients receiving RIC and allo-HCT.

TANDEM AUTOLOGOUS HCT FOR HODGKIN LYMPHOMA

Nonrandomized Studies
No RCTs have compared tandem autologous HCT with other standard of care therapies. One prospective, nonrandomized study has compared tandem to single autologous HCL for HL. Morschhauser et al (2008) and Sibon et al (2016) reported on the results of a prospective multicenter trial that evaluated a risk-adapted salvage treatment with single or tandem autologous HCT in 245 patients with relapsed or refractory HL.(26,27) Median follow-up time in the initial publication by Morschhauser et al (2008) was 51 months (range, 20-110 months). Sibon et al (2016) reported on the 10-year follow-up. Patients categorized as poor-risk (n=150) had primary refractory disease (n=77) or 2 or more of the following risk factors at first relapse: time to relapse less than 12 months, stage III or IV disease at the time of relapse, or relapse in previously irradiated sites (n=73). In this trial, these poor-risk patients were eligible for tandem autologous transplants. Intermediate-risk (n=95) patients, defined as one risk factor at relapse, were eligible for a single transplant. Overall, 70% of the poor-risk patients received tandem transplants, and 97% of the intermediate-risk patients received a single transplant.

Ninety-four poor-risk patients responded to cytoreductive chemotherapy (partial response or complete response [CR]), whereas 55 patients had the chemotherapy-resistant disease. A total of 137 patients (including the 94 patients with chemotherapy-sensitive disease and 43 of 55 with the chemotherapy-resistant disease) received the first autologous HCT. Among 121 patients who were fully restaged, 64 patients had achieved a complete response, 37 a partial response, and four had stable disease. These 105 patients then underwent a second autologous HCT after a median of 65 days. Among them, 80 patients achieved a complete response, including 17 patients who had achieved partial response and 3 patients with stable disease after the first transplant. Among the 55 patients who had cytoreduction failure, 30 responded to the first transplant (9 with complete response), and 17 achieved a complete response after the second transplant. Outcome analysis based on the intention-to-treat sample revealed that the five-year freedom from second failure and OS estimates were 73% and 85% for the intermediate-risk group and 46% and 57% for the poor-risk group, all respectively. At the 10-year follow-up reported by Sibon et al (2016),(27) freedom from second failure and OS rates were 64% (95% CI, 54% to 74%) and 70% (95% CI, 61% to 80%) for the intermediate-risk group, and 41% (95% CI, 33% to 49%) and 47% (95% CI, 39% to 55%) for the poor risk group.

In the poor-risk group, patients who underwent tandem transplant and had a CR to cytoreduction chemotherapy did not have superior outcomes compared with complete responders receiving a single transplant in previous studies by the same group.(28) However,

in this 2002 study, poor-risk patients who were partial responders and underwent tandem transplants did better compared with partial responders who received a single transplant in previous studies. In this study, five-year OS rates for poor-risk patients who completed the tandem transplant were 79% and 73% for complete and partial responders, whereas in a previous trial of single autologous HCT, five-year OS rates were 86% and 37% for complete and partial responders, all respectively.(28) The findings suggested that a single autologous HCT would be appropriate for intermediate-risk patients and for poor-risk patients who are complete responders to cytoreductive chemotherapy but that tandem autologous HCT showed a benefit in patients with chemotherapy-resistant disease and in partial responders to cytoreductive conditioning. The authors concluded that a trial randomizing patients to single vs tandem autologous HCT was unrealistic, given the low yearly incidence of poor-risk patients; in their estimation, the best possible comparisons would be with data from previous findings with single transplants.

Tandem autologous HCL for HL has also been evaluated in single-arm studies. Fung et al (2007) reported results from a pilot study on HL that evaluated the toxicities and efficacy of tandem autologous HCT in patients with primary refractory or poor-risk recurrent HL.(29) The study involved patients with primary progressive and 18 with recurrent HL who were enrolled in the study between 1998 and 2000. Patients had at least one of the following poor prognostic factors: first CR less than 12 months, extranodal disease, or B symptoms (presence of systemic symptoms) at relapse. Forty-one (89%) patients received the second transplant. With a median follow-up of 5.3 years (range, 1.6-8.1 years), the 5-year OS and PFS rates were 54% (95% CI, 40% to 69%) and 49% (95% CI, 34% to 63%), respectively. Additionally, Smith et al (2018) reported results from a more recent Phase II trial of 89 patients with primary progressive or recurrent HL conducted by the Southwest Oncology Group (SWOG) Clinical Trials Network.(12) This single-arm trial was conducted at 10 centers and enrolled patients between 2006 and 2009. Key patient characteristics included that 53% had induction failure, 18% had an initial response ≤ 12 months, 83% were stage III or IV at the time of trial enrollment, and 48% previously irradiated patients relapsed in an irradiated site. Eighty-two patients (92%) received the second transplant. With a median follow-up of 6.2 years, the 5-year PFS and OS rates were 55% (95% CI: 44%–64%) and 84% (95% CI: 74%–90%).

Section Summary: Tandem Autologous HCT for Hodgkin Lymphoma
There are no RCTs comparing tandem autologous HCT with alternatives for treating HL. One prospective, nonrandomized study reported that patients who had not achieved a CR after conventional chemotherapy had better outcomes with tandem HCT than with single HCT. However, the results of this trial were not definitive, and RCTs are needed to determine the efficacy of tandem transplants.

SUMMARY OF EVIDENCE

Autologous HCT
For individuals who have Hodgkin Lymphoma who receive autologous HCT as first-line therapy, the evidence includes RCTs. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality 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 that the technology results in an improvement in the net health outcome.

For individuals who have relapsed for refractory Hodgkin lymphoma who receive autologous HCT, the evidence includes RCTs, a meta-analysis, nonrandomized comparative studies, and case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, treatment-related mortality and morbidity. Two RCTs in patients with relapsed or refractory disease have reported a benefit in overall survival and a trend toward a benefit in overall survival. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have relapsed Hodgkin lymphoma after an autologous HCT who receive a second autologous HCT, the evidence includes case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. No RCTs or nonrandomized comparative studies were identified. In a case series, treatment-related mortality at 100 days was 11%; at a median follow-up of 72 months, the mortality rate was 73%. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Allo-HCT
For individuals who have HL who receive allo-HCT as first-line therapy, the evidence includes no published studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. No studies specifically addressing allo-HCT as first-line treatment for HL were identified. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have relapsed or refractory HL who receive allo-HCT, the evidence includes a number of case series and a meta-analysis. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality 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 overall survival rate of 83% and a 3-year overall survival rate of 50%. The evidence is sufficient to determine that the technology results in an 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. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. A 2016 meta-analysis of 38 case series found that a previous autologous HCT was significantly associated with higher one- and two-year overall survival 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 an improvement in the net health outcome.

For individuals who have relapsed or refractory Hodgkin lymphoma who receive reduced-intensity conditioning with allo-HCT, the evidence includes case series, cohort studies, and a systematic review. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality 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 an 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. 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 HCT might be higher than that 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 that the technology results in an improvement in the net health outcome.

Supplemental Information

CLINICAL INPUT RECEIVED THROUGH PHYSICIAN SPECIALTY SOCIETY AND ACADEMIC MEDICAL CENTERS

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2020
While the policy was under review (2020), Blue Cross Blue Shield Association sought clinical input to help determine whether the use of either second autologous hematopoietic cell transplantation for relapsed Hodgkin lymphoma or tandem autologous hematopoietic cell transplantation for Hodgkin lymphoma would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, Blue Cross Blue Shield Association received input from 4 respondents, including 3 complete responses including 2 physician-level responses identified through specialty societies and one physician-level response identified through an academic medical center.

Consensus determined that:
For individuals with relapsed Hodgkin lymphoma after an autologous hematopoietic cell transplantation who receive a second autologous hematopoietic cell transplantation, clinical input does not support a clinically meaningful improvement in net health outcome and does not indicate this use is consistent with generally accepted medical practice.

For individuals with Hodgkin lymphoma who receive tandem autologous hematopoietic cell transplantation, clinical input does not support a clinically meaningful improvement in net health outcome and does not indicate this use is consistent with generally accepted medical practice.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Radiology

In 2016, the American College of Radiology issued an Appropriateness Criteria on recurrent HL.(31) The criteria stated that while salvage therapy followed by autologous HCT is standard of care for relapsed HL, alternative therapies may be considered in select patients. For example, there is evidence that in patients with small, isolated relapses occurring more than 3 years after initial presentation, a course of radiotherapy or combined modality therapy without autologous HCT may be considered. Also, radiotherapy may be considered as part of combined modality therapy for patients with local relapse after treatment with chemotherapy alone or for relapses outside of the original site of disease.

American Society for Transplantation and Cellular Therapy

In 2015, guidelines were published by the American Society for Blood and Marrow Transplantation (now referred to as the American Society for Transplantation and Cellular Therapy) on indications for autologous and allogeneic HCT.(32) These guidelines were updated in 2020.(32) Recommendations described the current consensus on use of HCT in and out of the clinical trial setting. The 2015 and 2020 Society recommendations on HL are provided in Table 4.

Table 4. Recommendations for Use of HCT to Treat Hodgkin Lymphoma

Indication	Allogeneic HCT (2015 recommendation)	Allogeneic HCT (2020 recommendation)	Autologous HCT (2015 recommendation)	Autologous HCT (2020 recommendation)
Adult				
First complete response (PET negative)	Not generally recommended	Not generally recommended	Not generally recommended	Not generally recommended
First complete response (PET positive)	Not generally recommended	Subsection removed[a]	Standard of care, clinical evidence available	Subsection removed[a]
Primary refractory, sensitive	Standard of care, clinical evidence available	Standard of care, clinical evidence available	Standard of care	Standard of care
Primary refractory, resistant	Standard of care, clinical evidence available	Standard of care, clinical evidence available	Not generally recommended	Not generally recommended
First relapse, sensitive	Standard of care	Standard of care	Standard of care	Standard of care
First relapse, resistant	Standard of care, clinical evidence available	Standard of care, clinical evidence available	Not generally recommended	Not generally recommended
Second or greater relapse	Standard of care, clinical evidence available	Standard of care	Standard of care	Standard of care
Relapse after autologous transplant	Standard of care, clinical evidence available	Standard of care	Not generally recommended	Not generally recommended
Pediatric				
First complete response	Not generally recommended	Not generally recommended	Not generally recommended	Not generally recommended
Primary refractory, sensitive	Standard of care, clinical evidence available	Not generally recommended	Standard of care, clinical evidence available	Standard of care, clinical evidence available
Primary refractory, resistant	Standard of care, clinical evidence available	Standard of care, clinical evidence available	Not generally recommended	Not generally recommended

First relapse, sensitive	Standard of care, clinical evidence available	Not generally recommended	Standard of care, clinical evidence available	Standard of care
First relapse, resistant	Standard of care, clinical evidence available	Standard of care, clinical evidence available	Not generally recommended	Not generally recommended
Second or greater relapse	Standard of care, clinical evidence available	Standard of care, clinical evidence available	Standard of care, clinical evidence available	Standard of care, clinical evidence available

HCT: hematopoietic cell transplantation; PET: positron emission tomography.
[a]Subsection on positron emission tomography positive complete remission was removed because updated response criteria for these lymphoma essentially require normalization of [18F]2-fluoro-2-deoxy-D-glucose positron emission tomography to be assessed as a first complete remission.

The Society (2015) also published guidelines on the role of cytotoxic therapy with HCT in patients with Hodgkin Lymphoma.(23) Select recommendations are shown in Table 5.

Table 5. Recommendations on Use of Cytotoxic Therapy with HCT to Treat Hodgkin Lymphoma

Recommendation	GOR	Highest LOE
Autologous HCT		
Autologous HCT should not be offered as first-line therapy for advanced disease	A	1+
Autologous HCT should be offered as first-line therapy for patients who fail to achieve CR	B	2++
Autologous HCT should be offered as salvage therapy over nontransplantation (except localized disease or in patients with low-stage disease)	A	1+
Autologous HCT should be offered to pediatric patients with primary refractory disease or high-risk relapse who respond to salvage therapy	B	2++
Tandem autologous HCT is not routinely recommended in standard-risk patients	C	2+
Allogeneic HCT		
Allo-HCT should be used for relapse after ASCT instead of conventional therapy	B	2++
RIC is the recommended regimen intensity	B	2++
All donor sources can be considered	A	1+
There are limited data for tandem autologous HCT/allo-HCT	D	4
Allo-HCT is preferred over autologous HCT as second HCT (except in late relapse)	C	2+

allo: allogeneic; ASCT: autologous stem cell transplantation; CR: Complete response; GOR: grade of recommendation; HCT: hematopoietic cell transplantation; LOE: level of evidence; RIC: reduced-intensity conditioning.

National Comprehensive Cancer Network Guidelines

Current National Comprehensive Cancer Network (NCCN) guidelines for HL (v.3.2024) (4) include a recommendation for autologous or allogeneic HCT in patients with biopsy-proven refractory disease who have undergone second-line systemic therapy and are Deauville stage 5 according to restaging based on findings from positron emission tomography or computed tomography. Additionally, in patients with biopsy-proven refractory disease who have undergone second-line systemic therapy and are Deauville stage 1 to 3 according to restaging based on findings from positron emission tomography or computed tomography, high-dose therapy and autologous stem cell rescue plus either observation or brentuximab vendotin for 1 year is recommended for patients with high-risk of relapse.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 6.

Table 6. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03200977[a]	Safety of Allogeneic Hematopoietic Cell Transplantation (HCT) For Patients With Classical Hodgkin Lymphoma (CHL) Treated With Nivolumab	95	Dec 2022
Unpublished			
NCT00574496	An Intention-to-Treat Study of Salvage Chemotherapy Followed by Allogeneic Hematopoietic Stem Cell Transplant for the Treatment of High-Risk or Relapsed Hodgkin Lymphoma	30	Aug 2022
NCT01203020	Once Daily Intravenous Busulfex as Part of Reduced-toxicity Conditioning for Patients With Relapsed/Refractory Hodgkin's and Non-Hodgkin's Lymphomas Undergoing Allogeneic Hematopoietic Progenitor Cell Transplantation - A Multicenter Phase II Study	22	Sep 2021

NCT: national clinical trial
[a] Denotes an industry sponsored or cosponsored study

Government Regulations
National:

There are numerous autoimmune diseases and the Centers for Medicare and Medicaid Services have not issued a national coverage determination (NCD) for stem cell transplantation for each disease. CMS has a general NCD for stem cell transplantation.

Medicare National Coverage Determinations Manual 100-3, Chapter 1, Part 2, Section 110.23, "Stem Cell Transplantation." Effective date: 3/6/24; Implementation Date: 10/7/24

A. General

Stem cell transplantation is a process in which stem cells are harvested from either a patient's (autologous) or donor's (allogeneic) bone marrow or peripheral blood for intravenous infusion. Autologous stem cell transplantation (AuSCT) is a technique for restoring stem cells using the patient's own previously stored cells. AuSCT must be used to effect hematopoietic reconstitution following severely myelotoxic doses of chemotherapy (HDCT) and/or radiotherapy used to treat various malignancies. Allogeneic hematopoietic stem cell transplantation (HSCT) is a procedure in which a portion of a healthy donor's stem cell or bone marrow is obtained and prepared for intravenous infusion. Allogeneic HSCT may be used to restore function in recipients having an inherited or acquired deficiency or defect. Hematopoietic stem cells are multi-potent stem cells that give rise to all the blood cell types; these stem cells form blood and immune cells. A hematopoietic stem cell is a cell isolated from blood or bone marrow that can renew itself, differentiate to a variety of specialized cells, can mobilize out of the bone marrow into circulating blood, and can undergo programmed cell death, called apoptosis - a process by which cells that are unneeded or detrimental will self-destruct.

The Centers for Medicare & Medicaid Services (CMS) is clarifying that bone marrow and peripheral blood stem cell transplantation is a process which includes mobilization, harvesting, and transplant of bone marrow or peripheral blood stem cells and the administration of high dose chemotherapy or radiotherapy prior to the actual transplant. When bone marrow or peripheral blood stem cell transplantation is covered, all necessary steps are included in coverage. When bone marrow or peripheral blood stem cell transplantation is non-covered, none of the steps are covered.

Indications and Limitations of Coverage

- **Autologous STEM CELL Transplantation (AuSCT)**
  Effective for services performed on or after April 28, 1989, AuSCT is considered reasonable and necessary under §l862(a)(1)(A) of the Act for the following conditions and is covered under Medicare for patients with:
    - Advanced Hodgkin's disease who have failed conventional therapy and have no HLA-matched donor.
- **Other**
  All other indications for STEM CELL TRANSPLANTATION not otherwise noted above as covered or non-covered remain at local Medicare Administrative Contractor discretion.

Local:

There is no local coverage determination for Hodgkin's lymphoma.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- BMT – Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia
- BMT – Hematopoietic Cell Transplantation for Acute Myeloid Leukemia and Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)
- BMT – Hematopoietic Cell Transplantation for Autoimmune Diseases
- BMT – Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Cell Lymphocytic Lymphoma – Autologous or Allogeneic
- BMT – Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia
- BMT – Hematopoietic Cell Transplantation for CNS Tumors, Embryonal Tumors and Ependymoma
- BMT – Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer
- BMT – Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias (Allogeneic)
- BMT – Hematopoietic Cell Transplantation for Germ-Cell Tumors
- BMT – Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
- BMT – Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms
- BMT – Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
- BMT – Hematopoietic Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome
- BMT – Hematopoietic Cell Transplantation for Primary Amyloidosis
- BMT – Hematopoietic Cell Transplantation for Solid Tumors of Childhood
- BMT – Hematopoietic Cell Transplantation for Waldenström's Macroglobulinemia
- BMT – Malignant Astrocytomas and Gliomas (Autologous)
- Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant
- Orthopedic Applications of Stem-Cell Therapy (Including Allografts and Bone Substitutes used with Autologous Bone Marrow)

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through May 21, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/13	10/16/12	10/16/12	Topic split out from former combined JUMP policies: • Allogeneic (Allogenic) Bone Marrow/Stem Cell Umbilical Cord Blood Transplants Donor Lymphocyte Infusion (Established) • Autologous Bone Marrow or Blood-Derived Peripheral Stem Cell Transplantation (Established) • Tandem Autologous Bone Marrow/Stem Cell Transplants • Policy reformatted to mirror BCBSA. • Added “relative contraindications” to inclusionary/exclusionary section. • Removed deleted codes G0265, G0266 and G0267.
5/1/14	2/24/14	3/3/14	Updated CPT codes and references. Clarified inclusionary criteria. Policy status unchanged.
9/1/15	6/19/15	7/16/15	Updated rationale; policy status unchanged.
9/1/16	6/21/16	6/21/16	Routine maintenance
9/1/17	7/5/17	7/17/17	• Routine maintenance • “Stem” removed from HSCT, including title. • Guidelines on reduced-intensity allogeneic HCT changed to established for patients who would otherwise qualify for an allogeneic transplant.
9/1/18	6/19/18	6/19/18	Routine maintenance
11/1/19	8/20/19		Routine maintenance
11/1/20	9/30/20		• Routine maintenance • Autologous tandem HCT moved from established to exclusions based on specialist input

11/1/21	8/17/21		• Routine maintenance
11/1/22	8/16/22		• Routine maintenance
11/1/23	8/15/23		• Routine maintenance (slp) • Vendor Managed: N/A
11/1/24	8/20/24		• Routine maintenance (slp) • Vendor managed: N/A

Next Review Date: 3rd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: BMT - HEMATOPOIETIC CELL TRANSPLANTATION FOR HODGKIN LYMPHOMA

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	Refer to the Medicare regulations in the Government section of this policy
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.