Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 1/1/13**
(See policy history boxes for previous effective dates)

Title: BMT - Hematopoietic Stem-Cell Transplantation for Hodgkin Lymphoma

Description / Background

Hematopoietic Stem Cell Transplantation
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 radiation therapy.

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. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused 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 of allogeneic HSCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II loci on 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 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 prior to undergoing bone marrow ablation.

As a consequence, autologous HSCT is typically performed as consolidation therapy when the patient's disease is in complete remission (CR). Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

The conventional ("classical") practice of allogeneic HSCT 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 (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 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 allogeneic HSCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

Reduced-Intensity Conditioning for Allogeneic 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 traditional 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 non-relapse 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 allogeneic 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 Policy, the term reduced-intensity conditioning (RIC) will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (traditional) regimens.

Hodgkin Lymphoma

Hodgkin Lymphoma (HL) is a relatively uncommon B cell lymphoma. In 2011, the estimated number of cases in the U.S. is approximately 8,830 new diagnoses and 1,300 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 (WHO) classification divides HL into two main types (2):

1. "Classical" HL (CHL)
    - Nodular sclerosis
    - Mixed cellularity

    - Lymphocyte depleted
    - Lymphocyte rich
2. Nodular Lymphocyte-Predominant HL (NLPHL)

In Western countries, CHL accounts for 95% of cases of HL and NLPHL only 5%. (3) Classic HL 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.” (3)

The following staging system for HL 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 HL who can be treated with extended field radiation from those who require systemic chemotherapy.

Staging for Hodgkin Lymphoma
Staging for HL 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 including unexplained weight loss of more than 10% of body weight, unexplained fevers, or drenching night sweats. (3)

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 (non-regional) nodal involvement.

Patients with HL are generally classified into 3 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). (3)

Patients with non-bulky stage IA or IIA disease are considered to have clinical early-stage disease. These patients are candidates for chemotherapy, combined modality therapy, or

radiation therapy alone. (1) 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 radiation therapy. (1)

HL is highly responsive to conventional chemotherapy, and up to 80% of newly diagnosed patients can be cured with combination chemotherapy and/or radiation therapy. 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. (4)

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. (5) 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 HSCT but not more than 40% with early first relapse. (6)

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

Regulatory Status:

N/A

Medical Policy Statement

The safety and effectiveness of autologous or myeloablative allogeneic hematopoietic stem-cell transplantation (HSCT), reduced-intensity allogeneic HSCT, and tandem autologous HSCT have been established. They can be useful therapeutic options for patients with primary refractory or relapsed Hodgkin lymphoma (HL) who meet patient selection criteria.

Other uses for HSCT are experimental/investigational.

Contraindications

Absolute and relative contraindications represent situations where proceeding with transplant may not be advisable in the context of limited organ/tissue availability. Contraindications may evolve over time as transplant experience grows in the medical community. 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 recipients and have decided to proceed.

Relative contraindications:

The selection process for approved tissue transplants is designed to obtain the best result for each patient. Therefore, relative contraindications to HSCT 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).

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions:

Autologous or myeloablative allogeneic HSCT:

- Patients with primary refractory HL
- Patients with relapsed HL

Tandem autologous HSCT in patients:

- For patients who have failed a prior autologous HSCT used to treat primary refractory or relapsed HL
- In patients who would otherwise qualify for a myeloablative allogeneic transplant, but would be unable to tolerate a standard myeloablative conditioning regimen
- When insufficient stem cells are collected for an autologous HSCT.

Exclusions:

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

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	38208	38209	38210
38211	38212	38213	38214	38215	38220
38221	38230	38232	38240	38241	S2140
S2142	S2150				

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

N/A

Rationale

Autologous hematopoietic stem-cell transplantation for front-line therapy of Hodgkin lymphoma

A study published by Federico and colleagues concluded that high-dose chemotherapy (HDC) with autologous hematopoietic stem-cell transplantation (HSCT) offered no benefit in outcomes over conventional chemotherapy in front-line therapy for advanced Hodgkin lymphoma (HL) patients. (7)

Carella and colleagues reported the long-term results of 163 patients with unfavorable HL who had received either an autologous HSCT or additional standard chemotherapy for consolidation after initial conventional chemotherapy. (8) Patients were randomly assigned to receive HDC followed by an autologous HSCT (n=83) or 4 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 HSCT arm and 89% in the standard chemotherapy arm (p=0.6). Five-year overall survival (OS) was 88% (95% confidence interval [CI]: 80–96%) in the autologous HSCT arm and 88% (95% CI: 79–96%) in the CT arm (p=0.99). Ten-year OS was 85% (95% CI: 78–90%) versus 84% (95% CI: 77–89%) for the autologous HSCT versus the standard chemotherapy group, respectively. The authors concluded that, after a median follow-up of 107 months, their data supported that patients who respond to induction therapy with conventional chemotherapy do not achieve superior outcomes with consolidation with HDC and autologous HSCT.

Autologous HSCT for relapsed/refractory HL

Autologous HSCT is widely considered the therapy of choice for relapsed and refractory HL. Two randomized, controlled studies showed benefit in using autologous HSCT in these patients:

The British National Lymphoma Investigation (BNLI) study was the first to show a progression-free survival (PFS) benefit with autologous HSCT over conventional chemotherapy in relapsed or refractory HL patients. (9) Forty patients with relapsed or refractory HL were given chemotherapy without transplant (n=20) or autologous transplant after HDC (n=20). (10) A significantly better event-free survival (EFS) at 3 years of 53% versus 10% was reported in the patients who underwent transplant versus the group that did not.

Subsequently, these findings were confirmed in a larger trial by the German Hodgkin Study Group (GHSG) and European Group for Blood and EBMT. (11) Patients relapsing after initial chemotherapy were randomly assigned to chemotherapy without transplant or to autologous HSCT. In the final analysis of 144 patients, freedom from treatment failure at 3 years was 55% in the transplanted group versus 34% in the nontransplanted group. This benefit was maintained in subgroup analysis, regardless of early or late relapse, and the results were confirmed in follow-up data at 7 years. (12)

Several large retrospective studies have reported EFS rates ranging from 25–60%, with OS rates from 35–66%, showing that disease status before autologous HSCT was the most important prognostic factor for the final outcome. (4)
Limited treatment options exist for patients who relapse following an autologous HSCT and include single-agent palliative chemotherapy or occasionally, localized radiation therapy. (12)

When a further remission may be attained with conventional-dose chemotherapy, it is rarely durable, with a median OS of less than 1 year. (13) There is limited experience with second autologous HSCT, and treatment-related mortality is high (25–40%). (10) Smith and colleagues reported the outcomes of 40 patients (21 with HL and 19 with non-Hodgkin lymphoma [NHL]) who underwent a second autologous HSCT for relapsed lymphoma. (14) Results reported were combined for the two populations, but the authors state that the outcomes of patients with HL and NHL were similar. Median age at second HSCT was 38 years (range: 16–61). The second HSCT was performed more than 1 year after the first in 82%. Treatment-related mortality at day 100 post-transplant was 11% (95% CI: 3–22%). At a median follow-up of 72 months (range: 12–124 months) after the second HSCT, 73% of patients had died, 62% of these due to relapsed lymphoma. One-, 3-, and 5-year PFS probabilities were 50% (95% CI: 34–66%), 36% (95% CI: 21–52%), and 30% (95% CI: 16–46%), respectively. Corresponding OS probabilities were 65% (95% CI: 50–79%), 36% (95% CI: 22–52%), and 30% (95% CI: 17–46%), respectively. The authors stated that limitations to their study included the absence of an appropriate comparison group and that it was not known how many patients were considered for a second HSCT but were unable to mobilize sufficient stem cells or were otherwise unable to proceed to the second transplant. Finally, they stated that the heterogeneity of the preparative regimens used in this population precluded comparison of efficacy.

Allogeneic HSCT for HL
The application of allogeneic HSCT to the treatment of patients with HL initially appeared limited due to a procedure-related mortality rate of approximately 50% associated with the myeloablative conditioning regimen.

To date, most of the RIC allogeneic HSCTs have been performed in patients who have failed a previous autologous HSCT for primary relapsed/refractory HL, and most of the studies are characterized by small numbers of patients, disparate preparative and graft-versus-host disease (GVHD) prophylaxis regimens, and varying lengths of follow-up. Nonetheless, they have demonstrated reduced non-relapse mortality, and some suggest a graft-versus-HL effect with favorable disease control in these poor-prognosis patients.

Sarina and colleagues reported a retrospective study of 185 patients with HL who had failed an autologous HSCT. (15) One hundred twenty-two had donors available for a salvage RIC allogeneic HSCT; of these, 104 (85%) were transplanted. Sixty-three patients did not have a suitable donor and were treated with salvage chemotherapy or radiotherapy. Clinical characteristics between the two groups did not differ. After a median follow-up of 48 months, PFS and OS were better in the group that underwent the salvage allogeneic HSCT (39.3% vs. 14.2% and 66% vs. 42%, respectively; $p<0.001$), showing a survival benefit of an RIC allogeneic HSCT versus conventional treatment after a failed autologous HSCT for HL. This study supports one of the policy statements for RIC HSCT.

Peggs and colleagues investigated outcomes with reduced intensity conditioning (RIC) allogeneic HSCT and T cell depletion in multiply relapsed patients. (16) Forty-nine patients were enrolled, 90% of whom had failed a previous autologous transplant. Primary study endpoints were engraftment, toxicity, non-relapse-related mortality (NRM), and GVHD incidence. All patients achieved engraftment. Thirty-one patients had an HLA-matched donor and 18 an unrelated donor. The cumulative incidence of NRM was 4.1% at 100 days post-transplant and 16.3% at 730 days post-transplant. Patients with unrelated donors had a significantly higher NRM (34% vs. 7%) at 730 days. Projected 4-year OS and PFS were 56% and 39%, respectively.

Alvarez and colleagues reported the results of a Spanish Cooperative Protocol using RIC allogeneic HSCT in 40 patients with relapsed or refractory HL. (17) Seventy-three percent of patients had failed a previous autologous HSCT. Thirty-eight patients received hematopoietic cells from an HLA-identical sibling. One-year treatment-related mortality was 25%. OS and PFS were 48% and 32%, respectively, at 2 years. For patients who had failed a previous autologous HSCT, 2-year OS and PFS were 75% and 70%, respectively, in the subset that relapsed more than 12 months after autologous HSCT.

Todisco and colleagues evaluated the efficacy of RIC allogeneic HSCT in 14 patients with refractory or progressive HL after HDC and autologous HSCT. (13) All of the patients had received at least 1 prior course of HDC, and 50% had undergone 2 previous courses. The median time from the first and second courses of HDC and the RIC allogeneic HSCT was 15 and 8 months, respectively (range 2–34 and 2–31 months, also respectively). With a median follow-up of 21 months post-RIC allogeneic HSCT (range 3–74 months), 10 of the 14 patients were alive. Estimated OS at 1 and 2 years was 93% and 73%, respectively, for the entire population; 83% and 44%, respectively, for patients with chemotherapy-resistant disease; and 100% for those with chemotherapy-sensitive disease.

A review of the role of allogeneic HSCT in HL by Laport (18) summarizes the results of the most recent and largest studies of the use of RIC allogeneic HSCT for HL as follows: most patients have failed a prior autologous HSCT and are therefore heavily pretreated going into the RIC allogeneic HSCT; chemotherapy sensitivity is a reliable predictor of outcome; a matched versus an unmatched related donor did not affect survival in most reports; and approximately one-third to one-half of these patients may be cured with RIC allogeneic HSCT. EBMT published the results of the outcomes of 89 HL patients with relapsed or refractory disease who received an RIC allogeneic HSCT and were compared to 79 patients who received myeloablative conditioning. (19) Sixty-two percent of the RIC-group had undergone a previous autologous HSCT versus 41% of the patients in the myeloablative group. Although the incidence of relapse was nearly double in the RIC group (57% vs. 30%, respectively), after a median follow-up for surviving patients of 75 months (range, 12 to 120 months), 24 in the RIC group (26.9%) and 18 in the conventional group (22.8%) were alive. Five-year OS was 22% (95% CI: 13–31%) for the conventional group and 28% (95% CI: 18–38%) for the RIC group. Independent adverse prognostic factors for OS were a previously failed autologous HSCT (risk ratio [RR]: 1.59; 95% CI: 1.07 to 2.35; p=0.02), the use of myeloablative conditioning (RR: 1.62; 95% CI: 1.27-3.29; p=0.04), and the presence of refractory disease (RR: 1.51; 95% CI: 1.03–2.21; p=.003).

Anderlini and colleagues published the results of 58 patients from one institution with relapsed/refractory HL who received uniform conditioning regimens for RIC allogeneic HSCT.

(20) Fifty-seven percent of patients received their allograft from an unrelated donor. Eighty-three percent of patients had failed a prior autologous HSCT. Projected 2-year OS and PFS rates were 64% (range, 49–76%) and 32% (range, 20-45%), with 2-year disease progression/relapse at 55% (range, 43–70%). There were no statistically significant differences in OS, PFS, or disease progression/relapse between matched related and unrelated donor transplants.

Tandem (autologous-autologous) HSCT

Fung and colleagues reported results from a pilot study to evaluate the toxicities and efficacy of tandem autologous HSCT in patients with primary refractory or poor risk recurrent HL. (21) The study involved 28 patients with primary progressive and 18 with recurrent HL who were enrolled in the study between April 1998 and March 2000. Patients had at least one of the following poor prognostic factors: first CR less than 12 months, extranodal disease, or B symptoms at relapse. Forty-one patients (89%) received the second transplant. With a median follow-up of 5.3 years (range, 1.6-8.1), the 5-year OS and PFS were 54% (95% CI: 40–69%) and 49% (95% CI: 34–63%), respectively.

Morschhauser and colleagues reported on the results of a multicenter prospective trial that evaluated a risk-adapted salvage treatment with single or tandem autologous HSCT in 245 patients with relapsed/refractory HL. (22) Median follow-up time was 51 months (range, 20–110 months). Patients who were 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 occurring within previously irradiated sites (n=73). In this study, these poor-risk patients were eligible for tandem autologous transplants. Intermediate-risk patients (n=95), defined as 1 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. Overall, 94 poor-risk patients responded to cytoreductive chemotherapy (partial response [PR] or CR), whereas 55 patients had chemotherapy-resistant disease. A total of 137 patients (including the 94 patients with chemotherapy-sensitive disease and 43 of 55 with chemotherapy–resistant disease) received the first autologous HSCT. Among 121 patients who were fully restaged, 64 patients had achieved a CR, 37 a PR, and 4 had stable disease. These 105 patients then underwent the second autologous HSCT after a median of 65 days. Among them, 80 patients achieved a CR, including 17 patients who had achieved PR, 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 CR), and 17 achieved CR after the second transplant.

Outcome analysis based on the intent-to-treat sample showed 5-year freedom from second failure and OS were 73% and 85% for the intermediate-risk group and 46% and 57% for the poor-risk group, all respectively.

In the poor-risk group, patients who underwent tandem transplant and had a complete response to cytoreduction chemotherapy did not have superior outcomes compared to complete responders receiving a single transplant in previous studies. (23) However, in this study, poor-risk patients who were partial responders who underwent tandem transplants did better when compared to partial responders who received a single transplant in previous studies. In this study, 5-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 HSCT, 5-year OS rates were 86% and 37% for complete and partial responders, respectively. (23) The authors concluded that a single autologous HSCT is appropriate for intermediate-risk patients and for poor-risk patients who are complete responders to cytoreductive chemotherapy but that tandem autologous HSCT showed a benefit in patients with chemotherapy-resistant disease and in partial responders to cytoreductive conditioning. The authors stated that a trial of random assignment of single versus tandem autologous HSCT was unrealistic, given the low yearly incidence of poor-risk patients, and that the best possible comparisons are with data from previous findings with single transplants.

Clinical Trials and Guidelines
National Cancer Institute (NCI) database of clinical trials (Physician Data Query [PDQ®] database):

A randomized Phase III trial is closed studying combination chemotherapy with or without HSCT for men with previously untreated stage III or IV HL (NCT00005090). Estimated enrollment is 460.

An open-label, Phase III trial is active studying three different therapeutic strategies in patients with previously untreated HL, which includes one group of poor-prognosis patients who may or may not receive an autologous or allogeneic HSCT based on response to induction chemotherapy (NCT00920153). Estimated enrollment is 810, with an estimated primary completion date of May 2015.

Summary

- Randomized Phase 3 studies have shown that, in patients with relapsed or refractory Hodgkin lymphoma (HL), autologous HSCT leads to improved event- and progression-free survival and freedom from failure, versus conventional chemotherapy.
- The application of allogeneic HSCT to the treatment of patients with HL initially appeared limited due to a high procedure-related mortality rate. To date, most of the reduced intensity conditioning allogeneic HSCTs have been performed in patients who have failed a previous autologous HSCT for primary relapsed/refractory HL. Most of the studies are characterized by small numbers of patients, disparate preparative and graft-versus-host disease prophylaxis regimens, and varying lengths of follow-up. However, they have demonstrated reduced non-relapse mortality, and some suggest a graft-versus-HL effect with favorable disease control, and possible cure, in these poor-prognosis patients.
- A multicenter, prospective trial showed that tandem autologous HSCT (versus single autologous HSCT) may provide a survival benefit in select patients with poor-risk features.

Practice Guidelines and Position Statements
National Comprehensive Cancer Network (NCCN) Guidelines
The NCCN guidelines for HL (v.3.2011) include a category 2A recommendation for autologous HSCT in patients with progressive HL and in patients with relapse if initial stage was IA-IIA and the patient received no prior radiation and failed in initial sites only. Autologous HSCT is a category 1 recommendation for use in all other patients with relapsed HL. The guidelines state that allogeneic transplant is an option in select patients with progressive or relapsed disease as a category 3 recommendation and that allogeneic HSCT with reduced intensity conditioning remains investigational. The guidelines do not specifically address tandem transplants. (3)

Clinical Input Received through Physician Specialty Society and Academic Medical Center (October 2009)
In response to requests, Blue Cross Blue Shield Association received input from 2 academic medical centers while this policy was under review. 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.

The 2 reviewers agreed with the policy statements, with the exception of the use of a second autologous HSCT after a prior autologous HSCT, which both reviewers thought would be medically necessary in certain circumstances. The data to support the use of a second autologous HSCT is extremely limited, and the policy statement for this use of HSCT remains investigational.

Government Regulations

National:

National Coverage Determination (NCD) for Stem Cell Transplantation (110.8.1), Effective Date of this Version 8/4/10, Implementation Date 11/10/10, Retrieved from: http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=45&ncdver=5&bc=AgAAgAAAAAAA&, Accessed 7/25/12.

Indications and Limitations of Coverage

1. **Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)**
   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.
   a. Nationally Covered Indications
      The following uses of allogeneic HSCT are covered under Medicare:
      i. Effective for services performed on or after August 1, 1978, for the treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary,
      ii. Effective for services performed on or after June 3, 1985, for the treatment of severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome.
      iii. Effective for services performed on or after August 4, 2010, for the treatment of Myelodysplastic Syndromes (MDS) pursuant to Coverage with Evidence Development (CED) in the context of a Medicare-approved, prospective clinical study.

2. **Autologous Stem Cell Transplantation (AuSCT)**
   Autologous stem cell transplantation (AuSCT) is a technique for restoring stem cells using the patient's own previously stored cells.
   a. Nationally Covered Indications
      i. Effective for services performed on or after April 28, 1989, AuSCT is considered reasonable and necessary under §l862(a)(1)(A) of the Social Security Act (the Act) for the following conditions and is covered under Medicare for patients with:

- Acute leukemia in remission who have a high probability of relapse and who have no human leucocyte antigens (HLA)-matched;
- Resistant non-Hodgkin's lymphomas or those presenting with poor prognostic features following an initial response;
- Recurrent or refractory neuroblastoma; or
- Advanced Hodgkin's disease who have failed conventional therapy and have no HLA-matched donor.

ii. Effective October 1, 2000, single AuSCT is only covered for Durie-Salmon Stage II or III patients that fit the following requirements:
- Newly diagnosed or responsive multiple myeloma. This includes those patients with previously untreated disease, those with at least a partial response to prior chemotherapy (defined as a 50% decrease either in measurable paraprotein [serum and/or urine] or in bone marrow infiltration, sustained for at least 1 month), and those in responsive relapse; and,
- Adequate cardiac, renal, pulmonary, and hepatic function.

iii. Effective for services performed on or after March 15, 2005, when recognized clinical risk factors are employed to select patients for transplantation, high dose melphalan (HDM) together with AuSCT is reasonable and necessary for Medicare beneficiaries of any age group with primary amyloid light chain (AL) amyloidosis who meet the following criteria:
- Amyloid deposition in 2 or fewer organs; and,
- Cardiac left ventricular ejection fraction (EF) greater than 45%.

b. Nationally Non-Covered Indications

Insufficient data exist to establish definite conclusions regarding the efficacy of AuSCT for the following conditions:
- Acute leukemia not in remission;
- Chronic granulocytic leukemia;
- Solid tumors (other than neuroblastoma);
- Up to October 1, 2000, multiple myeloma;
- Tandem transplantation (multiple rounds of AuSCT) for patients with multiple myeloma;
- Effective October 1, 2000, non primary AL amyloidosis; and,
- Effective October 1, 2000, thru March 14, 2005, primary AL amyloidosis for Medicare beneficiaries age 64 or older.

In these cases, AuSCT is not considered reasonable and necessary within the meaning of §l862(a)(1)(A) of the Act and is not covered under Medicare.

B. Other

All other indications for stem cell transplantation not otherwise noted above as covered or non-covered nationally remain at local contractor discretion.

Local:

There is no local coverage determination.

Michigan Department of Community Health:

Medicaid Provider Manual, Version Date: April 1, 2012, Retrieved from http://www.mdch.state.mi.us/dch-medicaid/manuals/MedicaidProviderManual.pdf, Accessed: 7/25/12.

6.6 Transplants

Heart, bone marrow, liver, lung, simultaneous pancreas/kidney and pancreas transplants are reimbursed at the hospital's Medicaid cost to charge ratio.

- Organ acquisition costs are reimbursed at 100% of charges when billed using either revenue code 0811 or 0812. This applies to heart, kidney, liver, lung, simultaneous pancreas/kidney, or pancreas transplants. **This does not apply to bone marrow transplants. All bone marrow transplant charges are reimbursed at the hospital's cost to charge ratio.**
- The letter of authorization for the transplant from the Office of Medical Affairs (OMA) or MHP must be attached to all transplant claims, otherwise, payment is denied.
- Indicate "PA letter submitted" in the Remarks Section of the submitted claim.
- For other transplant services not described by a specific DRG, identify in the Remarks Section the type of transplant that has been performed (i.e., small bowel transplant).
- If the donor and beneficiary are both Medicaid eligible, the services must be billed under each beneficiary's respective ID Number. If only the beneficiary is Medicaid eligible, bill services for both donor and beneficiary under the Medicaid beneficiary's ID Number.

All other insurance resources must be exhausted before Medicaid is billed. If Medicare eligibility is denied, the denial notice must be submitted with the claim.

(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 – Autologous, for Malignant Astrocytomas and Gliomas
- BMT – Hematopoietic Stem Cell Transplantation for Breast Cancer
- BMT – Hematopoietic Stem Cell Transplantation for Treatment of Multiple Myeloma
- BMT – Hematopoietic Stem Cell Transplantation for Acute Lymphoblastic Leukemia
- BMT – Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia
- BMT – Hematopoietic Stem Cell Transplantation for Autoimmune Diseases
- BMT – Hematopoietic Stem Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma - Autologous or Allogeneic
- BMT – Hematopoietic Stem Cell Transplantation for Chronic Myelogenous Leukemia
- BMT – Hematopoietic Stem Cell Transplantation for CNS Embryonal Tumors and Ependymoma
- BMT – Hematopoietic Stem Cell Transplantation for Epithelial Ovarian Cancer
- BMT – Hematopoietic Stem Cell Transplantation for Miscellaneous Solid Tumors in Adults
- BMT – Hematopoietic Stem Cell Transplantation for Non-Hodgkin Lymphomas
- BMT – Hematopoietic Stem Cell Transplantation for Primary Amyloidosis
- BMT – Hematopoietic Stem Cell Transplantation for Solid Tumors of Childhood
- BMT – Hematopoietic Stem Cell Transplantation for Waldenström's Macroglobulinemia
- BMT – Hematopoietic Stem Cell Transplantation in the Treatment of Germ-Cell Tumors
- Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Stem-Cell Transplant

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through July 25, 2012, 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.

Next Review Date: 4th Qtr, 2013

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: BMT - HEMATOPOIETIC STEM-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 Medicare section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.
Blue Cross Complete of Michigan	Refer to Medicare section

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.