Kansas City
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Hematopoietic Stem-Cell Transplantation for Hodgkin Lymphoma

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Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for hematopoietic stem-cell transplantation for Hodgkin lymphoma when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

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

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

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

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

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

When Policy Topic is not covered

A second autologous stem-cell transplantation for relapsed lymphoma after a prior autologous HSCT is considered **investigational.**

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

Considerations

In the Morschhauser study of risk-adapted salvage treatment with single or tandem autologous hematopoietic stem-cell transplantation (HSCT) for first relapse or refractory Hodgkin lymphoma (HL) (reference 21), poor-risk relapsed HL was defined as 2 or more of the following risk factors at first relapse: time to relapse less than 12 months, stage III or IV at relapse, and relapse within previously irradiated sites. Primary refractory disease was defined as disease regression less than 50% after 4 to 6 cycles of doxorubicin-containing chemotherapy or disease progression during induction or within 90 days after the end of first-line treatment.

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for reduced-intensity conditioning (RIC) allogeneic HSCT. These include those with malignancies that are effectively treated with myeloablative allogeneic transplantation, but whose age (typically older than 55 years) or comorbidities (e.g., liver or kidney dysfunction, generalized

debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen.

The ideal allogeneic donors are HLA-identical matched siblings. Related donors mismatched at one locus are also considered suitable donors. A matched, unrelated donor identified through the National Marrow Donor Registry is typically the next option considered. Recently, there has been interest in haploidentical donors, typically a parent or a child of the patient, where usually there is sharing of only 3 of the 6 major histocompatibility antigens. The majority of patients will have such a donor; however, the risk of GVHD and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

Coverage will **not** be provided for:
- Transplant services when the cost is covered by government, foundation or charitable grants
- The purchase price of organs which are sold rather than donated to the recipient.
- An artificial organ

Reimbursement for Stem Cell collection and storage are considered payable under the Transplant Benefit when billed as a one-time, all-inclusive charge.

Transplant Benefit
The date on which the Transplant Benefit starts accumulating is determined by the transplant coordinator. The Transplant Benefit ends when the Transplant Lifetime Maximum benefit (if applicable) has been exhausted.

Benefits include:
- hospitalization of the recipient for medically recognized transplants from a donor to a transplant recipient;
- evaluation tests requiring hospitalization to determine the suitability of both potential (member's benefits must be verified with regard to the potential donor who does not turn out to be the actual donor) and actual donors, when such tests cannot be safely and effectively performed on an outpatient basis (**Note:** The member's benefits must be verified with regard to the **potential** donor who does not turn out to be the **actual** donor.);
- hospital room, board and general nursing in semi-private rooms;
- special care units, such as coronary and intensive care;
- hospital ancillary services;
- physicians' services for surgery, technical assistance, administration of anesthetics, and medical care;
- acquisition, preparation, transportation, and storage of organ / tissue / cells;
- diagnostic services;
- drugs which require a prescription by federal law;
- medical and surgical care of the donor (related to the procurement of the organ / tissue / cells) if coverage is not available to the donor from any other source. (Covered services provided to a donor will be applied against the recipient's transplant maximum benefit, if applicable)

If the donor and recipient are both listed on the same (family) policy, BCBSKC charges only one deductible and one coinsurance, if applicable.

In addition to the specific organ criteria, transplant candidates must also meet the following general criteria, including, but not limited to:
- Since compliance is a major factor in transplant graft survival, the patient (or legal guardian) must have the ability to accept and understand the transplant procedure and to maintain compliance with long-term medical management and immunosuppression.
- If applicable, patients with a history of malignancy must have passed the recommended length of time to be considered cured for that specific cancer. A complete metastatic evaluation must be performed before a patient will be considered an acceptable transplant candidate.

- Patients with a history of alcohol or substance abuse must have a six month history of abstinence as evidenced by negative urine or serum drug screens taken randomly.
- The patient must have adequate cardiopulmonary status.
- The patient must be free from active infection.

A covered person is eligible for retransplantation as deemed medically necessary and appropriate by BCBSKC. Review of a retransplantation request will include review of the covered person's compliance with relevant transplant selection criteria including, but not limited to, adherence to medication regimens, follow-up examinations and abstinence from the use of alcohol and drugs.

Clinical trials for conditions other than those allowed in this policy may be available in the research setting. However, these trials are considered investigational and/or experimental and therefore contract exclusions.

Note: There are some state mandates in place that require insurance carriers to cover certain clinical trials under very specific guidelines. Please contact your BCBSKC representative for more information.

Description of Procedure or Service

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 HCT) or from a donor (allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD). Cord blood is discussed in greater detail in a separate policy.

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. 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 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 2008, an estimated 8,220 new diagnoses and 1,350 deaths will occur in the U.S. (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 and older.

The 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 (NLPHL)

In Western countries, CHL accounts for 95% of cases of HL and NLPHL only 5%. (1) 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”. (1)

The following staging system for HL recognizes the fact 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. (1)

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

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

Stage III
Involvement of lymph node regions or structures on both sides of the diaphragm. These patients are further subdivided as follows:
III-1: disease limited to spleen or upper abdomen
III-2: periaortic or pelvic node involvement

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

Patients with 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 nonbulky 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. (3) 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. (3)

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 <12 months.

Rationale

This policy was originally created in 1999 and has been updated regularly with searches of the MEDLINE database. The most recent literature search, including EMBASE, was performed for the period September 1, 2012 through October 15, 2013.

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. (8)

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. (9) 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. (10) Forty patients with relapsed or refractory HL were given chemotherapy without transplant (n=20) or autologous transplant after HDC (n=20). (11) 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. (12) 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. (13)
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. (13) When a further remission may be attained with conventional-dose chemotherapy, it is rarely durable, with a median OS of less than 1 year. (14) There is limited experience with second autologous HSCT, and treatment-related mortality is high (25–40%). (11) 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. (15) 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. (16) 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. (17) 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. (18) 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. (14) 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 (19) 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.

The European Group for Blood and Marrow Transplantation (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. (20) 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. (21) 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.

Sureda and colleagues (22) reported the results of a Phase II study of 92 patients with relapsed HL and an HLA-identical sibling, a matched unrelated donor, or a one antigen mismatched, unrelated donor who were treated with salvage chemotherapy followed by RIC allogeneic transplantation. Fourteen patients had refractory disease and died from progressive lymphoma with a median OS after trial entry of 10 months (range, 6-17 months). Seventy-eight patients proceeded to allograft (unrelated donors, n=23). Fifty were allografted in complete or partial remission and 28 in stable disease. Non-relapse mortality rate was 8% at 100 days and 15% at 1 year. Relapse was the major cause of failure. The PFS rate was 47% at 1 year and 18% at 4 years from trial entry. For the allografted population, the PFS rate was 48% at 1 year and 24% at 4 years. Chronic graft-versus-host disease (GVHD) was associated with a lower incidence of relapse. Patients allografted in complete remission had a significantly better outcome. The OS rate was 71% at 1 year and 43% at 4 years.

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. (23) 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 complete remission (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. (7) 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. (24) 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. (24) 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):
An open-label, Phase III trial is actively 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.

A Phase III randomized study of induction chemotherapy followed by combination chemotherapy and autologous peripheral blood stem cell transplantation with or without high-dose sequential chemotherapy in patients with relapsed Hodgkin's lymphoma is recruitment status unknown. (NCT00025636) Estimated enrollment is 220.

Summary

- Randomized Phase 3 studies have shown that, in patients with relapsed or refractory Hodgkin lymphoma (HL), autologous hematopoietic stem-cell transplantation (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 Hodgkin lymphoma (HL) initially appeared limited due to a high procedure-related mortality rate. To date, most of the reduced intensity conditioning (RIC) 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 (GVHD) 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.2.2013) include a recommendation for autologous HSCT in patients with progressive and 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.

Clinical Input Received through Physician Specialty Society and Academic Medical Center (October 2009)

In response to requests, input was received 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.

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Billing Coding/Physician Documentation Information

38204 Management of recipient hematopoietic progenitor cell donor search and cell acquisition
38205 Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogenic
38206 Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207 Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208 Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing
38209 Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
38210 Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211 Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212 Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213 Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214 Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215 Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma,

mononuclear, or buffy coat layer
38220 Bone marrow; aspiration only
38221 Bone marrow; biopsy, needle or trocar
38230 Bone marrow harvesting for transplantation; allogeneic
38232 Bone marrow harvesting for transplantation; autologous
38240 Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241 Hematopoietic progenitor cell (HPC); autologous transplantation
86812 HLA typing; A, B, or C (eg, A10, B7, B27), single antigen
86813 HLA typing; A, B, or C, multiple antigens
86816 HLA typing; DR/DQ, single antigen
86817 HLA typing; DR/DQ, multiple antigens
86821 HLA typing; lymphocyte culture, mixed (MLC)
86822 HLA typing; lymphocyte culture, primed (PLC)
S2140 Cord blood harvesting for transplantation, allogeneic
S2142 Cord blood-derived stem-cell transplantation; allogeneic
S2150 Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days pre- and post-transplant care in the global definition.

Additional Policy Key Words

N/A

Policy Implementation/Update Information

12/1/01 New policy. Added to Surgery and Lab sections
12/1/02 No policy statement change
12/1/03 Policy statement revised to indicate that auto-HDC may be considered medically necessary in any patient with relapsed disease
12/1/04 No policy statement change. Added new G-codes. Added to Transplant section.
12/1/05 No policy statement change. Removed from Lab section.
4/1/06 Considerations section revised to include general criteria.
12/1/06 No policy statement changes.
12/1/07 No policy statement changes.
12/1/08 Policy updated with literature search; Description, Rationale, and Reference sections extensively updated, rewritten, revised. “High-dose chemotherapy” removed from title and policy statements reworded, but the policy statements remain otherwise unchanged.
12/1/09 No policy statement changes.
12/1/10 Policy statements added that tandem autologous SCT and reduced-intensity conditioning (RIC) allogeneic SCT may be considered medically necessary in specific situations and that a second autologous stem-cell transplantation for relapsed lymphoma after a prior autologous hematopoietic stem-cell transplant is considered investigational.
12/1/11 No policy statement changes.
1/1/12 Coding updated.
12/1/12 No policy statement changes.
12/1/13 No policy statement changes.
1/1/14 No policy statement changes.
