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Medical Policy Manual

Topic: Hematopoietic Stem-Cell Transplantation for Hodgkin Lymphoma

Date of Origin: May 2010

Section: Transplant

Last Reviewed Date: September 2013

Policy No: 45.30

Effective Date: January 1, 2014

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

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 gene loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

Conventional Preparative Conditioning for HSCT

The 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 develops 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 conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden, but also to minimize as much as possible associated treatment-related morbidity and 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 (conventional) regimens.

Hodgkin Lymphoma

Hodgkin Lymphoma (HL) is a relatively uncommon B-cell lymphoma. In 2012, there were an estimated 9,060 new diagnoses and 1,190 deaths in the U.S.[1] Two distinct age groups are affected by this disease

(indicating a bimodal distribution), those between the ages of 15 and 30 years, and, to a lesser extent, patients aged 55 and older.[2]

The World Health Organization (WHO) classification divides HL into two main types:[3]

- "Classical" HL (CHL)
    - Nodular sclerosis
    - Mixed cellularity
    - Lymphocyte depleted
    - Lymphocyte rich

- Nodular Lymphocyte-Predominant HL (NLPHL)

According to current guidelines from NCCN, CHL accounts for the vast majority (95%) of cases of HL in Western countries, with the remainder (5%) comprised of cases of NLPHL.[4] The guidelines go on to distinguish between the two types based upon the presence (CHL) or absence (NLPHL) of neoplastic Reed-Sternberg cells. NLPHL is also characterized by the presence of lymphocytic and histiocytic cells termed "popcorn cells."

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

The Ann Arbor staging system uses four stages (I-IV) to describe the progression of HL. Current NCCN guidelines describe the stages as the following:[4]

- "Stage I

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

- Stage II

  Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single associated extralymphatic organ or site and its regional lymph node(s) with or without involvement of other lymph node regions on the same side of the diaphragm (IIE). The number of lymph node regions involved should be indicated by a subscript (e.g., II2)

- 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."

Stages are further subdivided into A and B categories, with "B" indicating the presence of systemic symptoms such as substantive unexplained weight loss (greater than 10% of the body weight), unexplained fevers and drenching night sweats and "A" indicating the absence of any such systemic symptoms.[5] Patients with HL are generally classified into 3 groups: early-stage favorable (stage I–II with neither any B symptoms nor large mediastinal lymphadenopathy), early-stage unfavorable (stage I–II with large mediastinal mass, extranodal involvement, elevated erythrocyte sedimentation rate, involvement of three or more lymph node, or with B symptoms), and advanced-stage disease (stage III–IV).[6]

HL is highly responsive to conventional chemotherapy; however, 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.[7]

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.[8] 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.[9]

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.

MEDICAL POLICY CRITERIA

NOTE: This policy does not address non-Hodgkin lymphomas, chronic lymphocytic leukemia and small lymphocytic lymphoma, or Waldenstrom macroglobulinemia. These topics are considered separately in medical policies Transplant No. 45.23, 45.35, and 45.40, respectively.

I. Autologous hematopoietic stem cell transplantation (HSCT)

A. Medically necessary indications

A first autologous HSCT may be considered **medically necessary** for either of the following (1 or 2):

1. Primary refractory Hodgkin lymphoma (HL), defined as any of the following:

a. Disease regression of less than 50% after four to six cycles of anthracycline-containing chemotherapy

b. Disease progression during induction therapy

c. Disease progression within 90 days after the completion of first-line treatment

2. Relapsed HL without prior autologous HSCT

B. Investigational indications

Autologous HSCT is considered **investigational** for the following:

1. As initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for newly diagnosed disease to consolidate a first complete remission, or

2. A second autologous HSCT for relapsed lymphoma after a prior autologous HSCT

II. Allogeneic HSCT

A. Medically necessary indications

Myeloablative allogeneic HSCT may be considered **medically necessary** for either of the following (1 or 2):

1. Primary refractory Hodgkin lymphoma (HL), defined as any of the following:

a. Disease regression of less than 50% after four to six cycles of anthracycline-containing chemotherapy

b. Disease progression during induction therapy

c. Disease progression within 90 days after the completion of first-line treatment

2. Relapsed HL

B. Investigational indications

Myeloablative allogeneic HSCT is considered **investigational** as initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for newly diagnosed disease to consolidate a first complete remission.

C. Reduced intensity conditioning (RIC) allogeneic HSCT

RIC allogeneic HSCT may be considered **medically necessary** to treat HL when any of the following criteria are met (see further discussion in the Policy Guidelines):

1. Failed prior autologous HSCT used to treat primary refractory or relapsed disease, or

2. The patient would otherwise qualify for a myeloablative allogeneic transplant, but would be unable to tolerate a conventional myeloablative conditioning regimen, (see Policy Guidelines), or

3. The patient would otherwise qualify for a myeloablative allogeneic transplant, but insufficient stem cells are collected for an autologous HSCT

III. Tandem HSCT

A. Tandem HSCT is considered **medically necessary** for the following:

1. Primary refractory HL, defined as any of the following:

a. Disease regression of less than 50% after four to six cycles of anthracycline-containing chemotherapy

b. Disease progression during induction therapy

c. Disease progression within 90 days after the completion of first-line treatment

2. Relapsed disease with poor risk features in patients who do not attain a complete remission to cytoreductive chemotherapy prior to transplantation. Poor-risk relapsed HL is defined, based on the Morschhauser study,[10] as two or more of the following risk factors at first relapse:

a. Time to relapse less than 12 months

b. Stage III or IV at relapse

c. Relapse within previously irradiated sites

B. Tandem HSCT is considered **investigational** for the following

1. As initial therapy, or

2. For consolidation in first complete remission

Policy Guidelines

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, or 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.

SCIENTIFIC EVIDENCE

The principal outcomes associated with treatment of hematologic malignancies are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Risk of graft-versus-host disease is another primary outcome among patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT). Ideally, in order to understand the impact of HSCT for treatment of Hodgkin lymphoma, comparative clinical trials that compare this therapy to standard medical treatment, such as treatment with standard chemotherapy regimens, are needed. Further, for treatment of hematologic cancers, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits associated with treatment to understand the net treatment effect.

Autologous Hematopoietic Stem-Cell Transplantation (HSCT) for Front-Line Therapy of Hodgkin Lymphoma

Two non-randomized comparative studies have been published on the use of autologous HSCT versus additional standard chemotherapy as front-line therapy for advanced or unfavorable HL patients.[11,12] Neither study found a difference in overall survival at five years, nor was a treatment difference observed in the study which followed patients for ten years following treatment allocation.[12] Both sets of authors concluded that their respective results did not support the use of autologous HSCT over conventional chemotherapy for first-line treatment of HL.

Autologous HSCT for Relapsed/Refractory Disease

Autologous HSCT is widely considered the therapy of choice for relapsed and refractory HL. To date, two randomized controlled trials, and several non-randomized studies have been published on the use of single autologous HSCT for relapsed or refractory HL. Additional studies have been published on the use of a secondary autologous HSCT; however the studies had significant limitations including an inappropriate comparison groups and heterogeneity in preparative regimens.

Systematic Review

Two systematic reviews concluded autologous HSCT is beneficial for patients with relapsed/refractory Hodgkin lymphoma.

- In a 2013 Cochrane systematic review, Rancea and others investigated the best available treatment with high-dose chemotherapy (HDC) followed by autologous HSCT for patients with relapsed or refractory HL after first-line treatment.[13] Authors included three trials with 14 publications which included 398 patients. Authors concluded a progression-free survival (PFS) benefit for patients with relapsed or refractory Hodgkin lymphoma after first-line therapy who were treated with HDC followed by autologous HSCT compared to patients treated with conventional chemotherapy. In addition, authors determined a positive trend regarding OS, but more trials are needed to detect a

significant effect. Further, authors concluded that intensifying the HDC regime before HDC followed by autologous HSCT did not show a difference as compared to HDCT followed by autologous HSCT, but was associated with increased adverse events.

- A 2012 comparative effectiveness review by the Agency for Healthcare Research and Quality (AHRQ) considered the use of autologous HSCT in pediatric patients with relapsed or refractory disease.[2] Based upon available evidence (small, retrospective case series), the researchers concluded that, "Overall there appears to be a favorable risk-benefit profile for the treatment of Hodgkin's disease with HSCT in patients with progressive disease or relapse" and that among patients for whom autologous transplant is not an option, allogeneic transplant should be considered.

Randomized Controlled Trials (RCTs)

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 benefit with autologous HSCT over conventional chemotherapy in relapsed or refractory HL patients.[14] Forty patients with relapsed or refractory HL were given chemotherapy without transplant (n=20) or autologous transplant after HDC (n=20).[15] 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 Marrow Transplantation (EBMT).[16] Patients relapsing after initial chemotherapy were randomized 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.[17]

Non-randomized Trials

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.[7,18]

Limited treatment options exist for patients who relapse following an autologous HSCT, and include single-agent palliative chemotherapy or occasionally, localized radiation therapy.[17] When a further remission may be attained with conventional-dose chemotherapy, it is rarely durable, with a median OS of less than 1 year.[19] There is limited experience with second autologous HSCT, and treatment-related mortality is high (25%–40%).[15] 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.[20] 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 progression-free survival (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

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, 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. Examples of such studies include the following:

- Sarina and colleagues reported a retrospective study of 185 patients with HL who had failed an autologous HSCT.[21] 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 RIC allogeneic HSCT and T-cell depletion in multiply relapsed patients.[22] Forty-nine patients were enrolled, 90% of whom had failed a previous autologous transplant. Primary study endpoints were engraftment, toxicity, non-relapse-related mortality, and graft-versus-host-disease (GVHD) incidence. All patients achieved engraftment. Thirty-one patients had an HLA-matched donor and 18 an unrelated donor. The cumulative incidence of non-relapse-related mortality was 4.1% at 100 days post-transplant and 16.3% at 730 days post-transplant. Patients with unrelated donors had a significantly higher non-relapse-related mortality (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.[23] 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%, at 2 years, respectively. 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 high-dose chemotherapy and autologous HSCT.[19] All of the patients had received at least one prior course of HDC, and 50% had undergone two 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). 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.

- 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 a RIC allogeneic HSCT and were compared to 79 patients who received myeloablative conditioning.[24] 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%), 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 (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: 1.03–2.21; 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.[25] 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% (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 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.[26] 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 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.

A non-systematic review of the role of allogeneic HSCT in HL by Laport summarizes the results of the recent 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.[27]

Despite the non-randomized nature of available studies on allogeneic HSCT in patients with relapsed/refractory HL, comparative estimates of treatment effect are sufficient to suggest reduced non-relapse mortality and some suggest a graft-versus-HL effect with favorable disease control in these poor-prognosis patients.

Tandem (Autologous-Autologous) HSCT

Several pilot studies have evaluated the role of tandem autologous HSCT in treatment of HL:

- 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.[28] The study involved 28 patients with primary progressive and 18 with recurrent HL who were enrolled into the study between April 1998 and March 2000. Patients had at least one of the following poor prognostic factors: first complete remission 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 (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.[10] Median follow-up time was 51 months (range: 20–110 months). Patients were categorized as poor risk (n=150) if they had primary refractory disease (n=77) or two 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). Poor risk patients were eligible for tandem autologous transplants. Intermediate-risk patients (n=95), 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.

  Overall, 94 poor-risk patients responded to cytoreductive chemotherapy (partial or complete 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 three 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.

  Given the low yearly incidence of poor-risk HL patients, it may not be feasible to expect randomized clinical trials and that as such, comparisons with data from previous studies of single transplants may be a viable option. As such, poor-risk 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.[29] However, 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.[29] 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.

Due to the low incidence and quick progression of poor-risk HL disease, random assignment of single versus tandem autologous HSCT may not be a viable research option. In this context, available evidence is sufficient to suggest potential for treatment benefit in certain patients with tandem autologous HSCT.

Clinical Practice Guidelines

The 2013 National Comprehensive Cancer Network (NCCN) guidelines for Hodgkin Lymphoma (HL) include a category 2A recommendation for autologous HSCT in patients with relapsed/progressive HL.[4] The guidelines state that allogeneic transplant is an option in select patients with progressive or relapsed disease as a category 3 recommendation. The guidelines do not specifically address tandem transplants.

Summary

Autologous Hematopoietic Stem Cell Transplantation (HSCT)

- Randomized clinical trials 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 compared with conventional chemotherapy. Therefore, in these patients, autologous HSCT may be considered medically necessary.

- Available evidence suggests that autologous hematopoietic stem cell transplantation (HSCT) as first-line treatment for Hodgkin lymphoma (HL) does not improve survival outcomes and is therefore considered investigational.

Allogeneic HSCT

- The application of allogeneic hematopoietic stem cell transplantation (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 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. Therefore, in patients who have relapsed or refractory HL, allogeneic HSCT may be considered medically necessary.

- Due to high risk of treatment-related morality (estimated to be as high as 50%), allogeneic hematopoietic stem cell transplantation (HSCT) is considered investigational as a first-line treatment of Hodgkin lymphoma (HL).

Tandem HSCT

- A multicenter, prospective trial showed that, in patients with relapsed or refractory Hodgkin lymphoma (HL), tandem autologous hematopoietic stem cell transplantation (HSCT) may provide a

survival benefit compared with single autologous HSCT Therefore, in these patients, the use of tandem transplantation may be considered medically necessary.

- Due to lack of clinical trial data in the current scientific evidence, tandem hematopoietic stem cell transplantation (HSCT) is considered investigational as initial therapy, or for consolidation in first complete remission.

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Placental and Umbilical Cord Blood as a Source of Stem Cells, Policy No. 45.16

Hematopoietic Stem Cell Transplantation for Non-Hodgkin Lymphomas, Transplant, Policy No. 45.23

Hematopoietic Stem Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma, Transplant, Policy No. 45.35

Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis or Waldenstrom Macroglobulinemia, Transplant, Policy No. 45.40

CODES	NUMBER	DESCRIPTION
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal

CODES	NUMBER	DESCRIPTION
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;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	;autologous transplantation
	38243	;HPC boost
	38242	Allogeneic lymphocyte infusions
HCPCS	J9000–J9999	Chemotherapy drugs code range
	Q0083–Q0085	Chemotherapy administration code range
	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)