Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Transplant, Policy No. 45.30

Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Effective: July 1, 2019

Next Review: September 2019
Last Review: March 2019

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 cell transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

Notes:

- See Appendix I for glossary of terms.
- 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. A first autologous hematopoietic cell transplant for Hodgkin lymphoma may be considered **medically necessary** for any of the following:

A. Primary refractory disease, defined as one or more of the following:

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

2. Disease progression during induction therapy
3. Disease progression within 90 days after the completion of first-line treatment

B. Relapsed disease

II. Autologous hematopoietic cell transplantation for Hodgkin lymphoma is considered **investigational** for any of the following:

A. 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

B. A second autologous hematopoietic cell transplantation after a prior autologous hematopoietic cell transplantation.

III. Allogeneic hematopoietic cell transplantation (using either reduced intensity conditioning [RIC] or myeloablative conditioning) for Hodgkin lymphoma may be considered **medically necessary** for any of the following:

A. Primary refractory disease, defined as any of the following:

1. Disease regression of less than 50 percent after four to six cycles of anthracycline-containing chemotherapy
2. Disease progression during induction therapy
3. Disease progression within 90 days after the completion of first-line treatment

B. Relapsed disease

C. Failed prior autologous hematopoietic cell transplantation used to treat primary refractory or relapsed disease

IV. A second allogeneic hematopoietic cell transplantation is considered **investigational** for the treatment of Hodgkin lymphoma.

V. Allogeneic hematopoietic cell transplantation is considered **investigational** as initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for newly diagnosed Hodgkin lymphoma to consolidate a first complete remission.

VI. Tandem hematopoietic cell transplantation is considered **investigational** for the treatment of Hodgkin lymphoma**.**

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

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 three of the six 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.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, could impact our review and decision outcome.

- History and Physical/Chart Notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
2. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16
3. Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas, Transplant, Policy No. 45.23
4. Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma, Transplant, Policy No. 45.35
5. Hematopoietic Cell Transplantation for Primary Amyloidosis or Waldenstrom Macroglobulinemia, Transplant, Policy No. 45.40

BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION

Broadly speaking, there are two types of hematopoietic cell transplants (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease (e.g. lymphoma) with myeloablative doses of chemotherapy (with or without radiation) that are active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells 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 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 cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. 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 HCT

The conventional ("classical") practice of *allogeneic* HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant

cells and subsequent graft-versus-malignancy (GVM) effect that develops after engraftment of allogeneic 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 HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of *autologous* HCT is predicated on the ability of cytotoxic chemotherapy (with or without radiation) to be delivered at doses that could otherwise not be given without stem cells, which are infused to "rescue" hematopoiesis after high dose therapy. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission (CR). Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HCT

Reduced-intensity conditioning (RIC) refers to the conditioning with 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 HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells.

For 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 2008 World Health Organization (WHO) classification divides HL into two main types:[3]

- *Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)*
- *Classical Hodgkin lymphoma (CHL)*
  - Nodular sclerosis classical Hodgkin lymphoma
  - Lymphocyte-rich classical Hodgkin lymphoma
  - Mixed cellularity classical Hodgkin lymphoma

Lymphocyte-depleted classical Hodgkin lymphoma

In Western countries, CHL accounts for 95% of cases of HL and NLPHL, only 5%. Classic Hodgkin lymphoma 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.”

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 Hodgkin lymphoma is based on the Ann Arbor staging system. Patients with HL are generally classified into three 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). Each stage is subdivided into A and B categories. “A” indicates no systemic symptoms are present and “B” indicates the presence of systemic symptoms, which include unexplained weight loss of more than 10% of body weight, unexplained fevers, or drenching night sweats.[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.

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.[5]

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

Only approximately 25%-35% of patients with primary progressive or poor-risk recurrent HL achieve durable remission after autologous HCT, with most failures being due to disease progression after transplant. Most relapses after transplant occur within 1–2 years and once relapse occurs post-transplant, median survival is <12 months.

EVIDENCE SUMMARY

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 cell transplantation (HCT). Ideally, in order to understand the impact of HCT 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 CELL TRANSPLANTATION (HCT) FOR FRONT-LINE THERAPY OF HODGKIN LYMPHOMA

Two nonrandomized comparative studies, by Federico and Carella, have been published on the use of autologous HCT versus additional standard chemotherapy as front-line therapy for advanced or unfavorable HL patients.[8,9] 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.[9] Both sets of authors concluded that their respective results did not support the use of autologous HCT over conventional chemotherapy for first-line treatment of HL.

AUTOLOGOUS HCT FOR RELAPSED/REFRACTORY DISEASE

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

Systematic Reviews

In a 2013 Cochrane systematic review, Rancea investigated the best available treatment with high-dose chemotherapy (HDC) followed by autologous HCT for patients with relapsed or

refractory HL after first-line treatment.[10] Authors included three trials with 14 publications which included 398 patients. Authors concluded a PFS benefit for patients with relapsed or refractory Hodgkin lymphoma after first-line therapy who were treated with HDC followed by autologous HCT 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 HCT did not show a difference as compared to HDCT followed by autologous HCT, 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 HCT 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 HCT 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)

The British National Lymphoma Investigation (BNLI) study was the first to show a progression-free survival benefit with autologous HCT over conventional chemotherapy in relapsed or refractory HL patients.[11] Forty patients with relapsed or refractory HL were given chemotherapy without transplant (n=20) or autologous transplant after HDC (n=20).[12] A significantly better event-free survival (EFS) at three 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).[13] Patients relapsing after initial chemotherapy were randomized to chemotherapy without transplant or to autologous HCT. In the final analysis of 144 patients, freedom from treatment failure at three years was 55% in the transplanted group 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 seven years.[14]

Nonrandomized Studies

Several large retrospective studies have reported EFS rates ranging from 25%–60%, with OS rates from 35%–66%, showing that disease status before autologous HCT was the most important prognostic factor for the final outcome.[5,15]

Limited treatment options exist for patients who relapse following an autologous HCT, and include single-agent palliative chemotherapy or occasionally, localized radiation therapy.[14] When a further remission may be attained with conventional-dose chemotherapy, it is rarely durable, with a median OS of less than one year.[16] There is limited experience with second autologous HCT, and treatment-related mortality is high (25%–40%).[12] Smith and colleagues reported the outcomes of 40 patients (21 with HL and 19 with non-Hodgkin lymphoma [NHL]) who underwent a second autologous HCT for relapsed lymphoma.[17] 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 HCT was 38 years (range: 16–61). The second HCT was performed more than one 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 HCT, 73% of patients had died, 62% of these due to relapsed lymphoma. One-, three-, and five-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 HCT, 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.

While the above studies address Classic Hodgkin Lymphoma, only a limited number of studies have examined autologous HCT for relapsed/refractory nodular lymphocyte-predominant Hodgkin lymphoma. Among these is a recent retrospective study (Akhtar, 2018) with 60 patients that reported autologous HCT provided excellent disease control, with five-year PFS and OS of 66% and 87%, respectively.[18]

ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (HCT) FOR FRONT-LINE THERAPY OF HODGKIN LYMPHOMA

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

ALLOGENEIC HCT FOR HL FOR RELAPSED/REFRACTORY DISEASE

In 2016, Rashidi reported results from a meta-analysis of allogeneic cell transplantation (allo-SCT) in HL patients with end points at six-month, one-, two-, and three-year relapse-free survival (RFS) and overall survival (OS).[19] Data were pooled from 42 studies including 1850 patients. The pooled estimates (95% confidence interval) for six-month, one-year, two-year and three-year RFS were 77 (59-91)%, 50 (42-57)%, 37 (31-43)% and 31 (25-37)%, respectively. The corresponding numbers for OS were 83 (75-91)%, 68 (62-74)%, 58 (52-64)% and 50 (41-58)%, respectively. The authors concluded that over time, outcomes related to allo-SCT for HL have improved; their analyses indicated to survival plateau. Heterogeneity was found within the pooled studies, and the authors concluded their results indicate a need for improved allo-SCT treatment strategies.

Elshenawy (2018) performed a survival analysis of patients with Hodgkin lymphoma who failed HDC and autologous HCT.[20] The authors analyzed 137 HL patients (out of 347 transplanted patients) who experienced post autologous SCT failure. The 27 patients included in the analysis who received a second HCT (15 allogeneic, 2 auto) or brentuximab had significantly longer OS than other treatments (50.6 versus 22.5 months; $p<0.027$).

Reduced-Intensity Conditioning

To date, most of the reduced-intensity conditioning (RIC) allogeneic HCTs have been performed in patients who have failed a previous autologous HCT 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:

Gaudio (2019) retrospectively analyzed patients who received RIC allogeneic HCT for relapsed/refractory HL.[21] A total of 72 patients were include, of which 89% had had a previous autologous HCT. At 100 days post-transplant, 29 (43%) patients were in complete remission, 19 (28%) were in partial remission, 15 (22%) had stable disease, and 4 (6%) had progressive disease. Median follow-up was 48 months. Kaplan-Meier estimated five-year OS and PFS were 35% and 34%, respectively. Non-relapse mortality in the 20 months following transplant was 17%.

Sarina (2010) reported a retrospective study of 185 patients with HL who had failed an autologous HCT.[22] One hundred twenty-two had donors available for a salvage RIC allogeneic HCT; 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 HCT (39.3% vs. 14.2% and 66% vs. 42%, respectively; $p<0.001$), showing a survival benefit of an RIC allogeneic HCT versus conventional treatment after a failed autologous HCT for HL. This study supports one of the policy statements for RIC HCT.

Peggs (2005) investigated outcomes with RIC allogeneic HCT and T-cell depletion in multiply relapsed patients.[23] 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 four-year OS and PFS were 56% and 39%, respectively.

Alvarez (2006) reported the results of a Spanish Cooperative Protocol using RIC allogeneic HCT in 40 patients with relapsed or refractory HL.[24] Seventy-three percent of patients had failed a previous autologous HCT. 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 two years, respectively. For patients who had failed a previous autologous HCT, two-year OS and PFS were 75% and 70%, respectively, in the subset that relapsed more than 12 months after autologous HCT.

Todisco (2007) evaluated the efficacy of RIC allogeneic HCT in 14 patients with refractory or progressive HL after high-dose chemotherapy and autologous HCT.[16] 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 HCT was 15 and 8 months, respectively (range 2–34 and 2–31 months). With a median follow-up of 21 months post-RIC allogeneic HCT (range 3–74 months), 10 of the 14 patients were alive. Estimated OS at one and two 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 HCT and were compared to 79 patients who received myeloablative conditioning.[25] Sixty-two percent of the RIC-group had undergone a previous autologous HCT 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 HCT (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 (2008) published the results of 58 patients from one institution with relapsed/refractory HL who received uniform conditioning regimens for RIC allogeneic HCT.[26] Fifty-seven percent of patients received their allograft from an unrelated donor. Eighty-three percent of patients had failed a prior autologous HCT. Projected two-year OS and PFS rates were 64% (range: 49%–76%) and 32% (range: 20%-45%), with two-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 (2012) 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.[27] 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 one year. Relapse was the major cause of failure. The PFS rate was 47% at one year and 18% at four years from trial entry. For the allografted population, the PFS rate was 48% at one year and 24% at four 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 one year and 43% at four years.

A 2007 non-systematic review of the role of allogeneic HCT in HL by Laport summarizes the results of the recent studies of the use of RIC allogeneic HCT for HL as follows: most patients have failed a prior autologous HCT and are therefore heavily pretreated going into the RIC allogeneic HCT; 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 HCT.[28]

Despite the nonrandomized nature of available studies on allogeneic HCT 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. Retrospective comparisons of myeloablative vs reduced-intensity conditioning suggest an improvement in outcomes, including OS when RIC is used. Until randomized prospective trials are done, RIC conditioning is preferable in this setting.

TANDEM (AUTOLOGOUS-AUTOLOGOUS) HCT

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

Smith (2018) reported results of noncomparative study of tandem autologous HCT for relapsed/refractory HL.[29] Of 98 enrolled patients, 89 received the first transplant and 82 patients received both transplants and were included in the final analysis. The interval between day zero of the first and second transplant was between 28 and 60 days and the median follow-up was 5.4 years. There were no treatment-related deaths and 15 total deaths. The two-year and five-year PFS were 63% (95% CI 52 to 72%) and 55% (95% CI 44 to 64%) and two-year and five-year OS were 91% (95% CI 83 to 95%) and 84% (95% CI, 74% to 90%). Authors concluded that these results were promising compared to historical controls.

Morschhauser (2008) reported on the results of a multicenter prospective trial that evaluated a risk-adapted salvage treatment with single or tandem autologous HCT in 245 patients with relapsed/refractory HL.[30] 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 HCT. Among 121 patients who were fully restaged, 64 patients had achieved a CR, 37 a PR, and four had stable disease. These 105 patients then underwent the second autologous HCT 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 (nine with CR), and 17 achieved CR after the second transplant.

Outcome analysis based on the intent-to-treat sample showed five-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.

Fung (2007) reported results from a pilot study to evaluate the toxicities and efficacy of tandem autologous HCT in patients with primary refractory or poor risk recurrent HL.[31] 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 five-year OS and PFS were 54% (95% CI: 40–69%) and 49% (95% CI: 34–63%), respectively.

Ferme (2002) reported that 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.[32] 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, five-year OS rates for poor-risk patients who completed the tandem transplant were

79% and 73% for complete and partial responders, whereas in a previous trial of single autologous HCT, five-year OS rates were 86% and 37% for complete and partial responders, respectively.[32] The authors concluded that a single autologous HCT is appropriate for intermediate-risk patients and for poor-risk patients who are complete responders to cytoreductive chemotherapy, but that tandem autologous HCT showed a benefit in patients with chemotherapy-resistant disease and in partial responders to cytoreductive conditioning.

The evidence regarding the use of tandem transplant for Hodgkin lymphoma includes a small number of non-randomized studies. Due to the low incidence and quick progression of poor-risk HL disease, random assignment of single versus tandem autologous HCT may not be a viable research option. However, given the small number of studies and the efficacy of other treatments following transplant, further research is needed to demonstrate that the benefits of tandem transplant outweigh the risks. Therefore, the data on tandem transplants is insufficient to determine outcomes with this type of treatment.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) GUIDELINES

Guidelines from the National Comprehensive Cancer Network (NCCN) offer the following on the use of HCT in HL:[4] In CHL patients with refractory disease, high dose therapy and autologous stem cell rescue is included as an additional therapy option. Additionally:

> Allotransplant is an option in select patients as a category 3 recommendation. Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

AMERICAN COLLEGE OF RADIOLOGY

In 2016, the American College of Radiology issued an Appropriateness Criteria on recurrent HL.[33] The criteria stated that while salvage therapy followed by autologous HCT is standard of care for relapsed HL, alternative therapies may be considered in select patients. For example, there is evidence that in patients with small isolated relapses occurring more than three years after initial presentation, a course of radiotherapy or combined modality therapy without autologous HCT may be considered. Also, radiotherapy may be considered as part of combined modality therapy for patients with local relapse after treatment with chemotherapy alone or for relapses outside of the original site of disease.

AMERICAN SOCIETY FOR BLOOD AND MARROW TRANSPLANTATION

In 2015, guidelines were published by the American Society for Blood and Marrow Transplantation (ASBMT) on indications for autologous and allogeneic HCT.[34] Recommendations are intended to describe the current consensus on use of HCT within and outside of the clinical trial setting. Recommendations on Hodgkin lymphoma are provided in Table 1.

Table 1: ASBMT Recommendations for Hodgkin Lymphoma

Indication	Allogeneic HCT	Autologous
Adult		
First complete response (PET-)	N	N
First complete response (PET+)	N	C
Primary refractory, sensitive	C	S

Primary refractory, resistant	C	N
First relapse, sensitive	S	S
First relapse, resistant	C	N
Second or greater relapse	C	S
Relapse after autologous transplant	C	N
Pediatric		
First complete response	N	N
Primary refractory, sensitive	C	C
Primary refractory, resistant	C	N
First relapse, sensitive	C	C
First relapse, resistant	C	N
Second or greater relapse	C	C

ASBMT: American Society for Blood and Marrow Transplantation; C: clinical evidence available; HCT: hematopoietic cell transplantation; N: not generally recommended; S: standard of care.

In 2015, the ASBMT published the recommendations of their task force on the role of cytotoxic therapy with HCT in patients with Hodgkin Lymphoma.[35] Selected recommendations are shown in Table 2.

Table 2: Selected ASBMT Recommendations on Cytoxic Therapy with HCT for Hodgkin Lymphoma

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

ASCT: Autologous stem cell transplant; Allo-HCT: Allogeneic HCT; CR: Complete response; RIC: Reduced intensity conditioning

SUMMARY

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION (HCT)

There is enough research to show that in patients with relapsed or refractory Hodgkin lymphoma, autologous hematopoietic cell transplantation (HCT) leads to improved survival and freedom from failure compared with conventional chemotherapy. Therefore, in these patients, autologous HCT may be considered medically necessary.

Available research suggests that neither an autologous hematopoietic cell transplantation (HCT) as first-line treatment for Hodgkin lymphoma nor a second autologous HCT following a prior autologous HCT improve survival outcomes and are therefore considered investigational.

ALLOGENEIC HCT

The early research for allogeneic hematopoietic cell transplantation (HCT) as a treatment for patients with Hodgkin lymphoma (HL) shows high procedure-related mortality. Most of the reduced intensity conditioning allogeneic HCTs have been performed in patients who have failed a previous autologous HCT for primary relapsed/refractory HL. Most of the studies are characterized by small numbers of patients, differences in treatment approaches, and varying lengths of follow-up. However, the research has shown a reduction in mortality, and some studies suggest favorable disease control and possible cure, in these poor-prognosis patients. Therefore, in patients who have relapsed or refractory HL, allogeneic HCT may be considered medically necessary.

Due to high risk of treatment-related mortality, allogeneic hematopoietic cell transplantation (HCT) as a first-line treatment of Hodgkin lymphoma and subsequent allogeneic HCT *after* a previous allogeneic HCT are considered investigational**.**

TANDEM HCT

The research shows that in some patients with relapsed or refractory Hodgkin lymphoma (HL), tandem autologous hematopoietic cell transplantation (HCT) may provide a survival benefit compared with single autologous HCT. More research is needed to know for sure. No clinical guidelines based on research recommend tandem HCT for patients with HL. Therefore, in these patients, the use of tandem transplantation is considered investigational.

REFERENCES

1. Physician Data Query. General Information About Adult Hodgkin Lymphoma. Modified 08/15/2018. [cited 02/25/2019]; Available from: https://www.cancer.gov/types/lymphoma/hp/adult-hodgkin-treatment-pdq/
2. Ratko, TA, Belinson, SE, Brown, HM, et al. Hematopoietic Stem-Cell Transplantation in the Pediatric Population [Internet]. Rockville (MD): Agency for Healthcare Research and

Quality (US); 2012 Feb. (Comparative Effectiveness Reviews, No. 48.) [cited 3/11/2019] Available from: https://www.ncbi.nlm.nih.gov/books/NBK84626/. PMID: 22439159
3. Jaffe, ES. The 2008 WHO classification of lymphomas: implications for clinical practice and translational research. *Hematology / the Education Program of the American Society of Hematology American Society of Hematology Education Program*. 2009:523-31. PMID: 20008237
4. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Hodgkin Lymphoma. v.3.2018. [cited 2/25/2019]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf
5. Brice, P. Managing relapsed and refractory Hodgkin lymphoma. *Br J Haematol*. 2008 Apr;141(1):3-13. PMID: 18279457
6. Schmitz, N, Sureda, A, Robinson, S. Allogeneic transplantation of hematopoietic stem cells after nonmyeloablative conditioning for Hodgkin's disease: indications and results. *Semin Oncol*. 2004 Feb;31(1):27-32. PMID: 14970934
7. Schmitz, N, Dreger, P, Glass, B, Sureda, A. Allogeneic transplantation in lymphoma: current status. *Haematologica*. 2007 Nov;92(11):1533-48. PMID: 18024402
8. Federico, M, Bellei, M, Brice, P, et al. High-dose therapy and autologous stem-cell transplantation versus conventional therapy for patients with advanced Hodgkin's lymphoma responding to front-line therapy. *J Clin Oncol*. 2003 Jun 15;21(12):2320-5. PMID: 12805333
9. Carella, AM, Bellei, M, Brice, P, et al. High-dose therapy and autologous stem cell transplantation versus conventional therapy for patients with advanced Hodgkin's lymphoma responding to front-line therapy: long-term results. *Haematologica*. 2009 Jan;94(1):146-8. PMID: 19001284
10. Rancea, M, Monsef, I, von Tresckow, B, Engert, A, Skoetz, N. High-dose chemotherapy followed by autologous stem cell transplantation for patients with relapsed/refractory Hodgkin lymphoma. *The Cochrane database of systematic reviews*. 2013;6:CD009411. PMID: 23784872
11. Seftel, M, Rubinger, M. The role of hematopoietic stem cell transplantation in advanced Hodgkin Lymphoma. *Transfus Apher Sci*. 2007 Aug;37(1):49-56. PMID: 17716946
12. Linch, DC, Winfield, D, Goldstone, AH, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet*. 1993 Apr 24;341(8852):1051-4. PMID: 8096958
13. Schmitz, N, Pfistner, B, Sextro, M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. *Lancet*. 2002 Jun 15;359(9323):2065-71. PMID: 12086759
14. Murphy, F, Sirohi, B, Cunningham, D. Stem cell transplantation in Hodgkin lymphoma. *Expert Rev Anticancer Ther*. 2007 Mar;7(3):297-306. PMID: 17338650
15. Smith, SD, Moskowitz, CH, Dean, R, et al. Autologous stem cell transplant for early relapsed/refractory Hodgkin lymphoma: results from two transplant centres. *Br J Haematol*. 2011 May;153(3):358-63. PMID: 21410449
16. Todisco, E, Castagna, L, Sarina, B, et al. Reduced-intensity allogeneic transplantation in patients with refractory or progressive Hodgkin's disease after high-dose chemotherapy and autologous stem cell infusion. *Eur J Haematol*. 2007 Apr;78(4):322-9. PMID: 17253967
17. Smith, SM, van Besien, K, Carreras, J, et al. Second autologous stem cell transplantation for relapsed lymphoma after a prior autologous transplant. *Biol Blood Marrow Transplant*. 2008 Aug;14(8):904-12. PMID: 18640574

18. Akhtar, S, Montoto, S, Boumendil, A, et al. High dose chemotherapy and autologous stem cell transplantation in nodular lymphocyte-predominant Hodgkin lymphoma: A retrospective study by the European society for blood and marrow transplantation-lymphoma working party. *American journal of hematology*. 2018 Jan;93(1):40-6. PMID: 28971503
19. Rashidi, A, Ebadi, M, Cashen, AF. Allogeneic hematopoietic stem cell transplantation in Hodgkin lymphoma: a systematic review and meta-analysis. *Bone marrow transplantation*. 2016 Apr;51(4):521-8. PMID: 26726948
20. Elshenawy, MA, Shahzad Rauf, M, Elhassan, TAM, Maghfoor, I, Akhtar, S. Survival analysis of patients with Hodgkin lymphoma who failed high dose chemotherapy and autologous stem cell transplant. *Ann Hematol*. 2018;97(7):1229-40. PMID: 29484455
21. Gaudio, F, Mazza, P, Carella, AM, et al. Outcomes of Reduced Intensity Conditioning Allogeneic Hematopoietic Stem Cell Transplantation for Hodgkin Lymphomas: A Retrospective Multicenter Experience by the Rete Ematologica Pugliese (REP). *Clinical lymphoma, myeloma & leukemia*. 2019 Jan;19(1):35-40. PMID: 30293754
22. Sarina, B, Castagna, L, Farina, L, et al. Allogeneic transplantation improves the overall and progression-free survival of Hodgkin lymphoma patients relapsing after autologous transplantation: a retrospective study based on the time of HLA typing and donor availability. *Blood*. 2010 May 6;115(18):3671-7. PMID: 20220116
23. Peggs, KS, Hunter, A, Chopra, R, et al. Clinical evidence of a graft-versus-Hodgkin's-lymphoma effect after reduced-intensity allogeneic transplantation. *Lancet*. 2005 Jun 4-10;365(9475):1934-41. PMID: 15936420
24. Alvarez, I, Sureda, A, Caballero, MD, et al. Nonmyeloablative stem cell transplantation is an effective therapy for refractory or relapsed hodgkin lymphoma: results of a spanish prospective cooperative protocol. *Biol Blood Marrow Transplant*. 2006 Feb;12(2):172-83. PMID: 16443515
25. Sureda, A, Robinson, S, Canals, C, et al. Reduced-intensity conditioning compared with conventional allogeneic stem-cell transplantation in relapsed or refractory Hodgkin's lymphoma: an analysis from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol*. 2008 Jan 20;26(3):455-62. PMID: 18086796
26. Anderlini, P, Saliba, R, Acholonu, S, et al. Fludarabine-melphalan as a preparative regimen for reduced-intensity conditioning allogeneic stem cell transplantation in relapsed and refractory Hodgkin's lymphoma: the updated M.D. Anderson Cancer Center experience. *Haematologica*. 2008 Feb;93(2):257-64. PMID: 18223284
27. Sureda, A, Canals, C, Arranz, R, et al. Allogeneic stem cell transplantation after reduced intensity conditioning in patients with relapsed or refractory Hodgkin's lymphoma. Results of the HDR-ALLO study - a prospective clinical trial by the Grupo Espanol de Linfomas/Trasplante de Medula Osea (GEL/TAMO) and the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. *Haematologica*. 2012 Feb;97(2):310-7. PMID: 21993674
28. Laport, GG. Allogeneic hematopoietic cell transplantation for Hodgkin lymphoma: a concise review. *Leukemia & lymphoma*. 2008 Oct;49(10):1854-9. PMID: 18949609
29. Smith, EP, Li, H, Friedberg, JW, et al. Tandem Autologous Hematopoietic Cell Transplantation for Patients with Primary Progressive or Recurrent Hodgkin Lymphoma: A SWOG and Blood and Marrow Transplant Clinical Trials Network Phase II Trial (SWOG S0410/BMT CTN 0703). *Biol Blood Marrow Transplant*. 2018 Apr;24(4):700-7. PMID: 29289757

30. Morschhauser, F, Brice, P, Ferme, C, et al. Risk-adapted salvage treatment with single or tandem autologous stem-cell transplantation for first relapse/refractory Hodgkin's lymphoma: results of the prospective multicenter H96 trial by the GELA/SFGM study group. *J Clin Oncol*. 2008 Dec 20;26(36):5980-7. PMID: 19018090
31. Fung, HC, Stiff, P, Schriber, J, et al. Tandem autologous stem cell transplantation for patients with primary refractory or poor risk recurrent Hodgkin lymphoma. *Biol Blood Marrow Transplant*. 2007 May;13(5):594-600. PMID: 17448919
32. Ferme, C, Mounier, N, Divine, M, et al. Intensive salvage therapy with high-dose chemotherapy for patients with advanced Hodgkin's disease in relapse or failure after initial chemotherapy: results of the Groupe d'Etudes des Lymphomes de l'Adulte H89 Trial. *J Clin Oncol*. 2002 Jan 15;20(2):467-75. PMID: 11786576
33. Winkfield, KM, Advani, RH, Ballas, LK, et al. ACR Appropriateness Criteria(R) Recurrent Hodgkin Lymphoma. *Oncology (Williston Park, NY)*. 2016 Dec 15;30(12):1099-103, 106-8. PMID: 27987203
34. Majhail, NS, Farnia, SH, Carpenter, PA, et al. Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2015 Nov;21(11):1863-9. PMID: 26256941
35. Perales, MA, Ceberio, I, Armand, P, et al. Role of cytotoxic therapy with hematopoietic cell transplantation in the treatment of Hodgkin lymphoma: guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2015 Jun;21(6):971-83. PMID: 25773017
36. BlueCross BlueShield Association Medical Policy Reference Manual "Hematopoietic Cell Transplantation for Hodgkin Lymphoma." Policy No. 8.01.29

CODES

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
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)
	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	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)

APPENDIX I: Glossary of Terms used in this Policy

consolidation therapy[1] - Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.

relapse[2] - The return of a disease or the signs and symptoms of a disease after a period of improvement.

salvage therapy[3] - Treatment that is given after the cancer has not responded to other treatments.

tandem transplant[4] – Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

1. NCI Dictionary of Cancer Terms | https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45654 | Accessed Sept 25 2018
2. NCI Dictionary of Cancer Terms | https://www.cancer.gov/publications/dictionaries/cancer-terms?CdrID=45866 | Accessed Sept 25 2018
3. NCI Dictionary of Cancer Terms | https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=44176 | Accessed Sept 25 2018
4. NCCN Guidelines Version 1.2019 Multiple Myeloma | https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf | Accessed Sept 25 2018

Date of Origin: *May 2010*