Anthem

Medical Policy

Subject: Hematopoietic Stem Cell Transplantation for Hodgkin Disease and non-Hodgkin Lymphoma
Document #: TRANS.00028 **Publish Date:** 04/10/2024
Status: Revised **Last Review Date:** 02/15/2024

Description/Scope

This document addresses the use of hematopoietic stem cell transplantation and hematopoietic stem cell harvesting for treatment of Hodgkin disease and non-Hodgkin lymphoma.

Note:

- For umbilical cord transplantation, see TRANS.00016 Umbilical Cord Blood Progenitor Cell Collection, Storage and Transplantation for additional information and criteria.
- For transplantation for Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL), please refer to TRANS.00024 Hematopoietic Stem Cell Transplantation for Select Leukemias and Myelodysplastic Syndrome for information and criteria.

Position Statement

I. Hodgkin Disease

Medically Necessary

A. *An allogeneic (ablative and non-myeloablative) or autologous hematopoietic stem cell transplantation* is considered **medically necessary** for individuals with primary refractory Hodgkin disease or Hodgkin disease that has relapsed after an initial first remission (regardless of remission status at the time of transplant).
B. *An allogeneic hematopoietic stem cell transplantation after a prior autologous hematopoietic stem cell transplantation* is considered **medically necessary** for individuals with Hodgkin disease who meet the above criteria.
C. *A repeat autologous or allogeneic (ablative or non-myeloablative) hematopoietic stem cell transplantation* due to primary graft failure or failure to engraft is considered **medically necessary.**
D. *A planned tandem* autologous (autologous/autologous) hematopoietic stem cell transplantation* is considered **medically necessary** for risk-adapted salvage treatment for either primary refractive Hodgkin disease or individuals who have relapsed after standard therapy.

*Tandem transplantation refers to a planned infusion (transplant) of previously harvested hematopoietic stem cells with a repeat hematopoietic stem cell infusion (transplant) that is performed within 6 months of the initial transplant. This is distinguished from a repeat transplantation requested or performed more than 6 months after the first transplant, and is used as salvage therapy after failure of initial transplantation or relapsed disease.

Investigational and Not Medically Necessary:

A. *Allogeneic (ablative and non-myeloablative) hematopoietic stem cell transplantation or autologous hematopoietic stem cell transplantation* is considered **investigational and not medically necessary** for all other uses in Hodgkin disease including, but not limited to, initial therapy for newly diagnosed disease to consolidate a first complete remission (i.e., in individuals with a complete response to standard-dose induction therapy for newly diagnosed disease).
B. *A planned tandem* allogeneic (allogeneic/allogeneic) hematopoietic stem cell transplantation* is considered **investigational and not medically necessary.**
C. *A planned tandem autologous (autologous/autologous) hematopoietic stem cell transplantation* is considered **investigational and not medically necessary,** except when criteria above are met.
D. *A repeat autologous or allogeneic (ablative or non-myeloablative) hematopoietic stem cell transplantation* due to persistent, progressive or relapsed Hodgkin disease is considered **investigational and not medically necessary.**
E. *Hematopoietic stem cell harvesting* for a future but unscheduled transplant is considered **investigational and not medically necessary.**

II. non-Hodgkin Lymphoma (NHL)

Medically Necessary:

A. *Allogeneic (ablative and non-myeloablative) hematopoietic stem cell transplantation or autologous hematopoietic stem cell transplantation* is considered **medically necessary** to treat individuals with NHL subtypes classified by the National Cancer Institute (NCI) modified REAL classification system as “Indolent” in either of the following situations: *(see Rationale section for NCI classification)*
    1. As salvage therapy for those who do not achieve a complete remission (CR) after first-line treatment (induction) with a full course of standard-dose chemotherapy; **or**
    2. To achieve or consolidate a CR for those in a documented chemosensitive first or subsequent relapse, whether or not their lymphoma has undergone transformation to a higher grade.
B. *Allogeneic (ablative and non-myeloablative) hematopoietic stem cell transplantation or autologous hematopoietic stem cell transplantation* is considered **medically necessary** to treat individuals with NHL subtypes classified by the National Cancer Institute (NCI) modified REAL system as “Aggressive” in any of the following situations: *(see Rationale section for NCI classification)*
    1. As salvage therapy for those who do not achieve a complete remission (CR) after first-line treatment (induction) with a full course of standard-dose chemotherapy; **or**
    2. To consolidate a first CR for those with an International Prognostic Index (IPI) or age-adjusted IPI score that predicts a high- or high-intermediate risk of relapse *(see Rationale section for IPI score description)*;**or**

3. To consolidate a first CR for those with acute or lymphoma-type adult T-cell lymphoma/leukemia who have achieved a first remission; **or**
4. To achieve or consolidate a CR for those in a chemosensitive first or subsequent relapse.

C. *An autologous hematopoietic stem cell transplantation* is considered **medically necessary** to consolidate a first CR for individuals with mantle cell lymphoma. **Note:** criteria above or below may also apply to individuals with mantle cell lymphoma.

D. *An allogeneic (ablative or non-myeloablative) hematopoietic stem cell transplantation after a prior autologous hematopoietic stem cell transplantation* is considered **medically necessary** to treat individuals with NHL who meet the above criteria.

E. *A repeat autologous or allogeneic (ablative or non-myeloablative) hematopoietic stem cell transplantation* due to primary graft failure or failure to engraft is considered **medically necessary.**

F. *Hematopoietic stem cell harvesting** for an anticipated but unscheduled transplant is considered **medically necessary** in individuals who meet **all** of the following:
1. Follicular and low-grade non-Hodgkin lymphoma presenting with bone marrow involvement as documented by bone marrow biopsy/flow cytometry studies; **and**
2. Who meet the criteria above for transplant; **and**
3. The treating physician documents that a future transplant is likely; **and**
4. Harvesting is performed following chemotherapeutic treatment when the individual is in remission.

*__NOTE:__ Hematopoietic stem cell harvesting does not include the transplant procedure.

Investigational and Not Medically Necessary:

A. *Allogeneic (ablative and non-myeloablative) hematopoietic stem cell transplantation or autologous hematopoietic stem cell transplantation* is considered **investigational and not medically necessary** when criteria above are not met, including in the following situations:
1. As initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for all NHL; **or**
2. To consolidate a first CR for individuals with NHL subtypes classified by the National Cancer Institute (NCI) modified REAL system as “Aggressive” that does not meet the Medically Necessary criteria above.

B. *A planned tandem* allogeneic (allogeneic/allogeneic) hematopoietic stem cell transplantation* is considered **investigational and not medically necessary** as a treatment for individuals with NHL.

C. *A planned tandem* autologous (autologous/autologous) hematopoietic stem cell transplantation* is considered **investigational and not medically necessary** as a treatment for individuals with NHL.

D. *A repeat autologous or allogeneic (ablative or non-myeloablative) hematopoietic stem cell transplant* due to persistent, progressive or relapsed NHL is considered **investigational and not medically necessary**.

E. *Hematopoietic stem cell harvesting* for a future but unscheduled transplant is considered **investigational and not medically necessary** when the criteria above are not met.

*Tandem transplantation refers to a planned infusion (transplant) of previously harvested hematopoietic stem cells with a repeat hematopoietic stem cell infusion (transplant) that is performed within 6 months of the initial transplant. This is distinguished from a repeat transplantation requested or performed more than 6 months after the first transplant, and is used as salvage therapy after failure of initial transplantation or relapsed disease.

Rationale

Throughout the years, the methods to classify the various types of lymphomas have been modified as technology and understanding of the role of genetics and immunology have increased. The historical table of classifying NHL by the International Working Formulation (IWF) had been updated by the Revised European American Lymphoma (REAL) classification. Subsequently, the classification has been updated as a result of collaboration between the European and American hematology and pathology societies and World Health Organization (WHO). For clinical utility, NHL can also be divided into indolent or aggressive lymphomas (NCI, 2021). The use of a particular classification is based on the practitioner’s preference. A widely utilized tool as a prognostic indicator for NHL is the International Prognostic Indicator. The index was developed based on clinical characteristics to predict the outcome of aggressive NHL.

Individuals with indolent lymphoma may experience a relapse with a more aggressive histology. Documentation of conversion to a more aggressive histology requires an appropriate change to a therapy applicable to that histologic type. Histologic conversions or transformations are typically treated with the regimens prescribed for aggressive NHL (NCI, 2021).

Modified REAL Classification of Lymphoprolferative Diseases (NCL, 2021):
Non-Hodgkin
Indolent lymphoma/leukemia

A. Follicular lymphoma (follicular small cleaved cell [grade 1], follicular mixed small cleaved and large cell [grade 2], diffuse small cleaved cell)
B. Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)***(Refer to TRANS.00024 High-Dose Chemotherapy with Hematopoietic Stem Cell Transplantation for Select Leukemias and Myelodysplastic Syndrome)***
C. Lymphoplasmacytic lymphoma (Waldenström’s macroglobulinemia)
D. Extranodal marginal zone B-cell lymphoma (MALT lymphoma)
E. Nodal marginal zone B-cell lymphoma (monocytoid B-cell lymphoma)
F. Splenic marginal zone lymphoma (splenic lymphoma with villous lymphocytes)
G. Hairy cell leukemia
H. Mycosis fungoides/Sézary syndrome
I. T-cell granular lymphocytic leukemia
J. Primary cutaneous anaplastic large cell lymphoma/lymphomatoid papulosis (CD30+)
K. Nodular lymphocyte predominant Hodgkin lymphoma

Aggressive lymphomoa/leukemia

A. Diffuse large cell lymphoma (includes diffuse mixed cell, diffuse large cell, immunoblastic, T-cell rich large B-cell lymphoma) Distinguish:
1. Mediastinal large B-cell lymphoma
2. Follicular large cell lymphoma (grade 3)
3. Anaplastic large cell lymphoma (CD30+)
4. Extranodal NK/T-cell lymphoma, nasal type/aggressive NK-cell leukemia/blastic NK-cell lymphoma
5. Lymphomatoid granulomatosis (angiocentric pulmonary B-cell lymphoma)

6. Angioimmunoblastic T-cell lymphoma
7. Peripheral T-cell lymphoma, unspecified
    a. Subcutaneous panniculitis-like T-cell lymphoma
    b. Hepatosplenic T-cell lymphoma
8. Enteropathy-type T-cell lymphoma
9. Intravascular large B-cell lymphoma

B. Burkitt's lymphoma/Burkitt's cell leukemia/Burkitt's-like lymphoma
C. Precursor B- or T-cell lymphoblastic lymphoma/leukemia
D. Primary central nervous system (CNS) lymphoma
E. Adult T-cell leukemia/lymphoma (HTLV 1+)
F. Mantle cell lymphoma
G. Polymorphic post-transplantation lymphoproliferative disorder (PTLD)
H. AIDS-related lymphoma
I. True histiocytic lymphoma
J. Primary effusion lymphoma
K. B- or T-cell prolymphocytic leukemia
L. Plasmablastic lymphoma

International Prognostic Index (IPI)

- Age greater than 60 years
- Serum lactate dehydrogenase (LDH) concentration greater than normal
- ECOG performance status equal to 2
- Ann Arbor clinical stage III or IV
- Number of involved extranodal disease sites greater than 1

In this system, one point is given for each of the above characteristics present in the individual, for a total score ranging from zero to five, representing increasing degrees of risk:

- Low risk. IPI score of zero or one (0 to 1)
- Low intermediate risk. IPI score of two (2)
- High intermediate risk. IPI score of three (3)
- High risk. IPI score of four or five (4 to 5)

Age adjusted IPI
For this score, all of the prognostic factors listed above, with the exception of age and number of extranodal sites, were given one point, for a score ranging from zero to three, representing increased degrees of risk:

- Low risk. Age-adjusted IPI score of zero
- Low intermediate risk. Age-adjusted IPI score of one
- High intermediate risk. Age-adjusted IPI score of two
- High risk. Age-adjusted IPI score of three

Hodgkin Lymphoma

There are two main types of Hodgkin lymphoma: classic Hodgkin lymphoma and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). Classic Hodgkin lymphoma cases occur most often (95% of cases) in the Western countries (NCCN, 2024).

Modified REAL/WHO Classification of Lymphoproliferative Diseases (NCI, 2021):
Hodgkin Lymphoma

1. Nodular lymphocyte-predominant Hodgkin lymphoma
2. Classical Hodgkin lymphoma:
    a. Nodular sclerosis Hodgkin lymphoma
    b. Lymphocyte-rich classical Hodgkin lymphoma
    c. Mixed-cellularity Hodgkin lymphoma
    d. Lymphocyte-depleted Hodgkin lymphoma.

According to the National Comprehensive Cancer Network® (NCCN) Clinical Practice Guidelines Hodgkin Lymphoma (2024):

> The past few decades have seen significant progress in the management of HL. The advent of more effective treatment options has improved the 5-year survival rates, which have been unmatched in any other cancer over the past 4 decades. HL is among the most curable of malignancies with modern treatments, and newly diagnosed HL has a very high likelihood of being cured with appropriate management. In fact, cure rates for HL have increased so markedly that overriding treatment considerations often relate to long-term toxicity. Clinical trials still emphasize improvement in cure rates for patients with advanced disease, but the potential long-term effects of treatment remain an important consideration.

Autologous or allogeneic stem cell transplantation is recognized as a standard of care for refractory or relapsed Hodgkin disease in individuals who meet the criteria defined above (Anagnostopoulos, 2002; Berdeja, 2001; Chen, 2001).

Federico and colleagues (2003) reported results from 163 individuals randomized to high-dose chemotherapy with autologous stem cell transplantation (ASCT) (n=83) or to conventional chemotherapy (n=80) as part of the initial consolidative therapy. Five-year overall survival (OS) rates were 88% for both groups; 5-year relapse-free survival rate was 88% for the ASCT cohort and was not significantly different from 94% in the chemotherapy group (p=0.3). The authors concluded individuals with high-risk Hodgkin lymphoma who attained CR or partial response (PR) after four courses of chemotherapy have a favorable outcome with additional conventional chemotherapy. There was no documented benefit from the addition of autologous stem cell transplant to the consolidation regimen. Based on the literature and specialty consensus opinion, prophylactic harvest and storage of autologous stem cells for Hodgkin lymphoma is not considered standard therapy in first complete remission.

In a retrospective study, Moskowitz and colleagues (2009) noted autologous stem cell transplant (ASCT) for primary refractory or relapsed Hodgkin lymphoma had resulted in 5-year progression free survival (PFS) of 50%. However, progressive disease after transplant is the most common cause of ASCT failure with median survival ranging from 7.3 to 25 months.

The NCCN Clinical Practice Guidelines in Oncology for Hodgkin lymphoma (NCCN, 2024) panel provides a category 1 recommendation for High-dose therapy and autologous stem cell rescue (HDT/ASCR) as the best option for individuals with Hodgkin Lymphoma (HL) that is not cured with primary treatment.

Non-Hodgkin Lymphoma

The majority of studies examining the use of autologous or allogeneic stem cell transplantation as a treatment for indolent and aggressive NHL are nonrandomized uncontrolled case series. These studies had failure-free survival rates ranging from 44% to 63% for an estimated 3- to 4-year period, which are comparable to the survival rates reported by the studies using conventional chemotherapy (Gopal, 2002; Hahn, 2001; Williams, 2001). Early trials using autologous hematopoietic stem cell transplants as salvage therapy for relapsed aggressive NHL demonstrated a significant benefit from transplant compared to standard chemotherapy (Greb, 2008). With newer chemotherapeutic agents and monoclonal antibodies, the use of stem cell transplantation in various stages of NHL increased.

Autologous stem cell transplantation is being studied as first-line therapy for aggressive lymphoma and for other clinical indications. Greb and colleagues (2008) performed a systematic review and meta-analysis to determine the effects of autologous hematopoietic stem cell transplant as first-line therapy for aggressive non-Hodgkin lymphoma versus standard chemotherapy. Included in this analysis were 2728 individuals randomized in 15 different trials. Based on 2126 participants in 14 studies, the relative risk to achieve CR was 1.11 with high dose-chemotherapy and transplant favored. However, the authors noted there was no significant difference in OS between the conventional chemotherapy cohort compared to the transplant group. In a subgroup analysis, there was a statistically significant difference (p=0.032) between the good- and poor-risk individuals. The cohort with good-risk age-adjusted IPI reported impaired OS with transplant and the poor-risk group demonstrated significant effects favoring transplant. From the 14 trials reporting mortality data, the treatment-related mortality (TRM) and the mortality during treatment (MDT) rate was 5.7% for the stem cell transplant group versus 4.3% for those receiving standard chemotherapy. The authors concluded:

> There is no evidence that high-dose chemotherapy with stem cell transplant (HDC/SCTT) improves OS when compared to conventional chemotherapy in the first-line treatment of individuals with aggressive NHL. However, there is some evidence that HDC/SCT might be detrimental in individuals with good risk.

The American Society for Transplantation and Cellular Therapy, formerly the American Society for Blood and Marrow Transplantation, (ASTCT, 2011), issued guidelines for use of high-dose chemotherapy with hematopoietic stem cell transplantation as treatment for diffuse large cell B-cell (DLBCL) non-Hodgkin lymphoma. Stem cell transplant is more effective than standard chemotherapy and is recommended treatment for the following indications:

- first chemotherapy-sensitive relapse;
- first complete remission in high/intermediate-high risk IPI individuals;
- as high-dose, sequential therapy in intermediate-high/high risk IPI untreated individuals.

Vigouroux and colleagues (2007) reported long-term survival was improved in a retrospective, multicenter study of 73 subjects with relapsed or refractory low-grade lymphoma treated with reduced intensity chemotherapy and allogeneic stem cell transplant. Data was stratified based on the disease status prior to the transplant, with 21 individuals having a CR, 33 individuals with a PR and 19 individuals identified as chemoresistant. Cumulative treatment related events were 32% for those in CR, 28% for PR and 63% for chemoresistant individuals. At a median follow-up of 37 months, the 3-year event-free survival rates were 66%, 52% and 32% respectively and a relapse rate of 9.6%. Despite the morbidities, the 3-year overall survival rates for the different cohorts were 66%, 64% and 32% in individuals with CR, PR and chemoresistant disease.

The FL2000 collaborative phase III trial compared individuals with follicular lymphoma (FL) treated with first-line treatment with R-CHVP-I (rituximab, cyclophosphamide, doxorubicin, etoposide and prednisolone) and CHVP-I. Le Gouill and colleagues (2011) analyzed the data on the 175 of the 358 participants in the FL2000 trial who had relapsed or refractory disease. Choice of second-line therapy was at the discretion of the treating physician. Salvage therapy included various chemotherapy regimens, 90Y ibritumomab tiuxetan, CD20-targeted monoclonal antibodies or anti-CD22 monoclonal antibody therapy. Forty-two participants (24%) had high dose chemotherapy with autologous stem cell transplant (HDC-ASCT) at first relapse. The median follow-up was 31 months (0-64 months) which was calculated from the time of progression or relapse. The investigators noted the OS rates at 3 years was 92% with HDC-ASCT (95% confidence interval [CI], 78-97%) compared to 63% without HDC-ASCT (95% CI, 51-72%; P=0.0003). The respective event-free survival (EFS) rates for 3 and 5 years were 50% (95% CI, 42-58%) and 26% (95% CI, 14-39%), respectively. The EFS rate in those treated with HDC-ASCT was 73% (95% CI 56- 84%) compared to 39% (95% CI, 29-50%) without transplant (P=0.005). The authors note the longer EFS and OS in the transplanted participants demonstrate the favorable impact of HDC-ASCT in first relapse or refractory disease compared to non-transplanted participants.

Primary Central Nervous System Lymphoma

Primary central nervous system lymphoma (PCNSL) is a rare and aggressive subtype of NHL affecting the brain, spinal cord, cerebrospinal fluid and/or eyes without systemic involvement. Nearly 90% of PCNSLs are CD20-positive DLBCLs. The remaining cases are comprised of other cell types including low-grade lymphomas, T cell lymphomas, and Burkitt lymphoma confined to the CNS. It has been estimated that, in 2022, approximately 25,050 individuals in the United States would be diagnosed with a PCNS tumor, and that these tumors would result in approximately 18,280 deaths. Although survival for CNS cancers has improved in recent decades, less improvement has been seen for older adults. This may be related to a higher incidence of glioblastoma in this population. PCNSL is also seen in approximately 7-15% of individuals with PTLDs, a condition that is associated with a poor prognosis (NCCN CNS Cancers, 2023).

Historically, PCNSL was treated predominantly with whole brain radiation therapy, however, treatment has evolved over the years. Now, treatment generally consists of two phases: induction to achieve remission and consolidation to prevent disease recurrence. Although NCCN cites phase II trials showing that consolidative therapy with HDC-ASCT is feasible and well tolerated, they also note a lack of evidence showing improved outcomes with this treatment. According to the NCCN:

> There are currently no conclusive prospective data published comparing consolidation with high-dose chemotherapy regimens or high-dose chemotherapy with autologous stem cell transplantation versus maintenance therapy or observation, and there are different approaches at different institutions. Consolidation with high-dose chemotherapy and autologous stem cell transplant is frequently considered for fitter patients. Eligibility criteria used in the respective trials that studied these regimens need to be carefully considered when considering this approach, and referral to centers with subspecialty expertise in PCNSL should be considered (NCCN CNS Cancers, 20230).

For additional guidance on the management of individuals with PCNSL, the NCCN recommends the user refer to their clinical practice guidelines on DLBCL (found in the NCCN B-Cell Lymphoma Clinical Practice Guidelines).

Mantle Cell Lymphoma

Mantle cell lymphoma is a mature B-cell lymphoma which may present with asymptomatic advanced disease like indolent lymphomas. However, based on a shorter median survival when compared to other lymphomas, mantle cell lymphoma is now considered to be an aggressive lymphoma (NCI, 2021). In a risk-adapted retrospective study with 121 participants, Tam (2009) noted an improved

progression-free survival (PFS) of 39% and OS 61% at a median follow-up of 6 years in individuals treated with autologous stem cell transplantation in first remission.

Based on improved PFS and OS rates in various studies, the NCCN CPG for B-Cell Lymphoma (2024) recommends autologous stem cell transplantation as consolidation therapy for individuals with Mantle cell lymphoma in remission.

Adult T-cell Lymphoma/Leukemia

Adult T cell leukemia-lymphoma (ATL) is a peripheral T-cell neoplasm associated with infection by the human T-lymphotropic virus, type I (HTLV-1). While it is considered a very aggressive non-Hodgkin T-cell lymphoma variant, the disease course varies considerably and is sometimes relatively indolent. According to the Shimoyama criteria, there are four different clinical variants of ATL: acute, lymphoma-type (lymphomatous), chronic, and smoldering; Each of the clinical variants appear to have differing genomic alterations, differing clinical courses, and may require a different course of treatment.

- Acute – Individuals usually present with systemic symptoms such as lymphadenopathy, organomegaly, an elevated lactate dehydrogenase (LDH) level, and circulating malignant cells. Survival with treatment is generally measured in terms of months to a year. Four-year survival ranges from 5 to 10% and median survival is approximately 8 to 10 months when treated with regimens designed for advanced, aggressive non-Hodgkin lymphoma.
- Lymphoma-type – Individuals with this variant usually present with prominent lymphadenopathy but do not have blood involvement. Prognosis is poor, similar to that of individuals with the acute variant.
- Chronic – Individuals with this variant typically present with skin lesions, mild lymphadenopathy, and leukocytosis with an absolute lymphocytosis that may remain stable for months to years. Median survival for individuals in this group is 2 to 5 years. However, there is a subcategory of individuals with unfavorable chronic-type ATL which is distinguished by low serum albumin, high LDH, or high blood urea nitrogen concentration. Individuals in this subgroup have a poor prognosis similar to individuals with the acute and lymphoma variants.
- Smoldering – Individuals with this clinical variant may be asymptomatic except for frequent pulmonary and/or skin lesions. They typically have normal blood lymphocyte counts with less than 5% circulating neoplastic cells and normal calcium levels. Median survival of individuals in this group who do not receive treatment is approximately 3 years.

Individuals with typical chronic or smoldering ATL are managed with watchful waiting until symptoms develop because conventional chemotherapy does not appear to improve their survival. When symptoms develop, these individuals can be managed with skin-directed therapies for skin lesions as recommend for individuals with Sézary syndrome. Immediate treatment is generally offered to individuals with acute, lymphoma-type, or unfavorable chronic-type ATL. Because there “are no optimal standard treatment regimens for the management of ATLL”, the NCCN recommends all individuals with ATLL enroll in clinical trials (NCCN T-Cell Lymphoma, 2024).

The NCCN also recommends that:

> Patients with acute ATLL that is not responding to initial therapy should be treated with an alternate regimen not previously used for first-line therapy for ATLL or best supportive care. Second-line therapy or best supportive care are included as options for patients with lymphoma subtype that is not responding to initial therapy. In patients with acute or lymphoma subtypes who achieve a response to second-therapy, allogeneic hematopoietic stem cell transplant (HSCT) should be considered if a donor is available (NCCN T-Cell Lymphoma, 2024).

Tandem Transplantation

The evidence to support the use of a planned tandem autologous (autologous/autologous) stem cell transplantation and a tandem autologous/allogeneic stem cell transplant consisting of an autologous stem cell transplant followed by an allogeneic or nonmyeloablative allogeneic stem cell transplant in individuals with Hodgkin disease and non-Hodgkin lymphoma is limited. In a review of various case series and phase II nonrandomized trials, Papadopoulos and colleagues (2001) describe the difficulty in determining safety and efficacy from the small trials and the multiple variables. The different types of transplants, various preparatory regimens and disease states made conclusions difficult to generalize. A study by Haioun (2001) was unable to show significant improvement in event free survival with tandem autologous stem cell transplantation in 36 consecutive high-risk individuals with NHL.

In a phase II, prospective, uncontrolled trial, Morschhauser (2008) and colleagues investigated single or tandem autologous stem cell transplantation (ASCT) as a risk-adapted salvage treatment for 245 individuals with Hodgkin lymphoma and treatment failure to first-line therapy. Participants were stratified according to the assessment at the onset of second-line therapy. Risk factors used to stratify participants following first relapse are listed below:

1. Time to relapse less than 12 months;
2. Stage III or IV at relapse;
3. Relapse within previously irradiated sites.

The poor-risk group included 150 individuals with either primary refractory disease (n=77) or two or more of the risk factors listed above (n=73). This poor-risk group was eligible for tandem ASCT. The intermediate-risk group included 95 individuals with only one of the three risk factors listed above upon relapse. This group was eligible for single ASCT. Participants in both groups were treated with cytoreductive therapy prior to ASCT. Median follow-up was 51 months (20-110 months).

Overall, 94 poor-risk participants responded to cytoreductive chemotherapy (partial or complete response) while 55 participants had chemotherapy resistant disease. A group of 137 poor-risk participants (participants older than 50 years were excluded) which included the 94 with chemo-sensitive disease and 43 of the 55 with chemotherapy-resistant disease received the first autologous HSCT. Of those, 121 were restaged and 64 achieved a CR, 37 a PR and 4 had stable disease. These 105 participants (70% of all eligible poor-risk participants) received a second ASCT after a median of 65 days which included 30 of 55 of those participants with primary refractory disease. Of those receiving the second transplant (n=105), 80 achieved a CR including 17 participants who had achieved PR and 3 participants with stable disease after the first transplant. Of the 55 participants who had originally had cytoreduction failure, 30 responded to the first transplant, 9 with a CR, and 17 achieved a CR after the second transplant.

Using an intent-to-treat analysis, 5-year freedom from second failure (FF2F) and OS were 73% and 85% for the intermediate group and 46% and 57% for the poor-risk group. In the poor-risk group, participants who were treated with a tandem transplant and had a CR to cytoreduction chemotherapy did not have a better outcome than complete responders receiving a single ASCT in earlier studies (Ferme 2002). However, poor-risk participants who were partial responders and underwent tandem transplant did better than partial responders receiving a single ASCT in earlier trials. The 5-year OS for poor-risk participants who had tandem transplant were 79% for complete and 73% for partial responders while a previous trial of single ASCT showed a 5-year OS of 86% for complete and only 37% for partial responders (Ferme 2002). Overall, transplant-related mortality was 4% in the poor risk group. The authors concluded that single ASCT is appropriate for intermediate-risk HL participants and for individuals with poor risk HL that are complete responders to cytoreductive chemotherapy. However, tandem ASCT was felt to be more beneficial than single ASCT for individuals with poor-risk

HL that are either chemotherapy resistant or only partial responders to cytoreductive chemotherapy. These investigators acknowledge the study was not a randomized controlled comparison of single versus tandem ASCT in poor-risk participants. However, they contend that a randomized controlled trial comparing single versus tandem ASCT in poor-risk participants was not likely given the small numbers of poor-risk participants available for study and that comparison of the results of this study with previous findings with single ASCT provides useful information regarding which poor-risk participants are more likely to benefit from tandem ASCT.

Specialty consensus opinion considers tandem autologous hematopoietic stem cell transplantation as salvage treatment for either primary refractive Hodgkin disease or individuals who have relapsed after standard therapy as medically necessary.

Poor Graft Function

Poor graft function or graft failure is one of the major causes of morbidity and mortality after hematopoietic stem cell transplantation. Poor graft function is defined as slow or incomplete recovery of blood cell counts following a stem cell transplant or decreasing blood counts after initially successful hematopoietic engraftment following a stem cell transplant. There are various options for the management of poor graft function. Stem cell “boost” is a non-standardized term that is used to describe an infusion of additional hematopoietic stem cells to an individual who has undergone a recent hematopoietic stem cell transplantation and has poor graft function (Larocca, 2006). The infusion of additional hematopoietic stem cells is to mitigate either graft failure or rejection with or without immunosuppression. This process may include the collection of additional hematopoietic stem cells from a donor and infusion into the transplant recipient. Note that a "boost" is distinct from a repeat transplant and that there may be separate medical necessity criteria for a repeat transplant.

Other considerations

Hematopoietic stem cell transplant (HSCT) is an important therapeutic modality for many malignant and nonmalignant hematologic diseases and its applicability continues to expand as its use in established therapies is refined and new indications are identified. In addition, the number of individuals who could benefit from HSCT has increased due to advancements, such as reduced intensity conditioning regimens, which have made HSCT safer (Majhail, 2015). However, the risks associated with transplant-associated morbidity and mortality remain significant. Most transplant centers utilize forums, boards or conferences where the treatment options of individual HSCT candidates are discussed (Majhail, 2015). Okamoto (2017) notes:

> The medical decision-making process for a transplant procedure is complex which requires assessing several factors besides the underlying indication for transplantation. Those include patient/disease factors, and transplant factors such as planed conditioning/graft-versus-host disease (GVHD) prophylaxis and stem cell source. Patient factors include their overall health and comorbidities, prior therapies, and how patients responded to those therapies, age, and disease/disease risk.

There are a number of clinical assessment and prognostic tools which evaluate individuals based upon multiple factors. The earlier, simpler tools, such as the Charlson Comorbidity Index (CCI) were useful in predicting outcomes, but lacked the sensitivity of subsequent tools such as the HCT-specific comorbidity index (HCT-CI) The HCT-CI score has been validated in multiple HSCT settings to independently predict non-relapse mortality (NRM) rates by weighting 17 relevant comorbidities. The HCT-CI was further enhanced by the incorporation of some laboratory biomarkers into an augmented version.

While these tools provide valuable prognostic information, the decision to transplant is unique to each individual and needs to include a specific risk-benefit analysis in partnership with the individual’s physicians and other caregivers.

Background/Overview

Hodgkin Disease (also known as Hodgkin Lymphoma)

In Hodgkin disease, cells in the lymphatic system grow abnormally and may spread beyond the lymphatic system. As the disease progresses, it compromises the body's ability to fight infection. Many initial signs and symptoms may be similar to those of influenza, such as fever, fatigue and night sweats. Eventually, tumors develop. Hodgkin disease most commonly affects people between the ages of 20 and 39 and people older than age 65. The NCI reports chemotherapy and radiation therapy may cure more than 75% of all newly diagnosed Hodgkin disease. Advances in diagnosis, staging and treatment of Hodgkin disease have helped to make this once uniformly fatal disease highly treatable with the potential for full recovery. The national mortality rate for adult Hodgkin Lymphoma has fallen more rapidly than for any other malignancy over the last 5 decades (NCI, 2021).

Classical Hodgkin lymphoma (CHL) is distinguished by the presence of an abnormal Reed-Sternberg cell in the lymphoma tissue. Lymphocyte-predominant Hodgkin lymphoma (LPHL) accounts for approximately 5% of all Hodgkin lymphoma cases. Lymphocyte predominant cells, also called “popcorn cells” are present in the lymphoma tissue instead of the Reed-Sternberg cells (NCCN Hodgkin Lymphoma, 2024).

non-Hodgkin Lymphoma

NHL is a collection of more than a dozen different cancers of the lymphatic system, which generates the body's immune defenses. This system includes a network of channels akin to blood vessels through which lymphocytes--important white blood cells of the immune system--patrol the body for invading microbes. Along these lymphatic routes in the neck, armpits, abdomen, and groin are clusters of bean-shaped lymph nodes that house platoons of the infection-fighting lymphocytes. These cells also cluster in areas that serve as gateways to the body, including the mucous membranes lining the respiratory and digestive tracts, and the skin. Lymphocytes travel in the bloodstream, as well. The lymphatic system also includes such organs as the spleen, thymus and tonsils.

According to the National Cancer Institute (NCI, 2021), NHL can be divided into two prognostic groups: the indolent lymphomas and the aggressive lymphomas. Indolent NHL types have a relatively good prognosis with a median survival from 8 to 15 years, but they usually are not curable in advanced clinical stages. Early stage (stage I and stage II) indolent NHL can be effectively treated with radiation therapy alone. Most of the indolent types are nodular (or follicular) in morphology. The aggressive type of NHL has a shorter natural history, but a significant number of these individuals can be cured with intensive combination chemotherapy regimens. In general, with modern treatment of individuals with NHL, overall survival at 5 years is over 60%. Of individuals with aggressive NHL, more than 50% can be cured. The vast majority of relapses occur in the first 2 years after therapy. The risk of late relapse is higher in individuals with a divergent histology of both indolent and aggressive disease.

Indolent NHL is usually responsive to immunotherapy, radiation therapy and chemotherapy, with a continuous rate of relapse normally seen in advanced stages of the disease. However, a continuous rate of relapse is usually seen in advanced stages. Individuals can be re-treated with considerable success as long as the disease histology remains low grade. Those who present with or convert to aggressive forms of NHL may have sustained complete remissions with combination chemotherapy regimens or aggressive consolidation with marrow or stem cell support (NCI, 2021).

The modified REAL/WHO classification utilizes three major categories of lymphoid malignancies based on morphology and cell

lineage: B-cell neoplasms, T-cell/natural killer (NK)-cell neoplasms and Hodgkin lymphoma.

Updated REAL/WHO Classification for non-Hodgkin Lymphoma (NCI, 2021)

B-cell neoplasms

A. Precursor B-cell neoplasm: precursor B-acute lymphoblastic leukemia/lymphoblastic lymphoma (LBL)
B. Peripheral B-cell neoplasms
    1. B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
    2. B-cell prolymphocytic leukemia
    3. Lymphoplasmacytic lymphoma/immunocytoma
    4. Mantle cell lymphoma
    5. Follicular lymphoma
    6. Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphatic tissue (MALT) type
    7. Nodal marginal zone B-cell lymphoma (± monocytoid B-cells)
    8. Splenic marginal zone lymphoma (± villous lymphocytes)
    9. Hairy cell leukemia
    10. Plasmacytoma/plasma cell myeloma
    11. Diffuse large B-cell lymphoma
    12. Burkitt lymphoma

T-cell and putative NK-cell neoplasms

A. Precursor T-cell neoplasm: precursor T-acute lymphoblastic leukemia/LBL
B. Peripheral T-cell and NK-cell neoplasms
    1. T-cell chronic lymphocytic leukemia/prolymphocytic leukemia
    2. T-cell granular lymphocytic leukemia
    3. Mycosis fungoides/Sézary syndrome
    4. Peripheral T-cell lymphoma, not otherwise characterized
    5. Hepatosplenic gamma/delta T-cell lymphoma
    6. Subcutaneous panniculitis-like T-cell lymphoma
    7. Angioimmunoblastic T-cell lymphoma
    8. Extranodal T-/NK-cell lymphoma, nasal type
    9. Enteropathy-type intestinal T-cell lymphoma
    10. Adult T-cell lymphoma/leukemia (human T-lymphotrophic virus [HTLV] 1+)
    11. Anaplastic large cell lymphoma, primary systemic type
    12. Anaplastic large cell lymphoma, primary cutaneous type
    13. Aggressive NK-cell leukemia

Hematopoietic stem cell transplantation is a process which includes mobilization, harvesting, and transplant of stem cells after the administration of high dose chemotherapy (HDC) and/or radiotherapy. High-dose chemotherapy involves the administration of cytotoxic agents using doses several times greater than the standard therapeutic dose. In some cases, whole body or localized radiotherapy is also given and is included in the term HDC when applicable. The rationale for HDC is that many cytotoxic agents act according to a steep dose-response curve. Thus, small increments in dosage will result in relatively large increases in tumor cell kill. Increasing the dosage also increases the incidence and severity of adverse effects related primarily to bone marrow ablation (e.g., opportunistic infections, hemorrhage, or organ failure). Bone marrow ablation is the most significant side effect of HDC. As a result, HDC is accompanied by a re-infusion of hematopoietic stem cells, which are primitive cells capable of replication and formation into mature blood cells, in order to repopulate the marrow. The potential donors of stem cells include:

1. ***Autologous -*** Stem cells can be harvested from the individual's own bone marrow prior to the cytotoxic therapy
2. ***Allogeneic -*** Stem cells harvested from a healthy, histocompatible donor. (Note: this document does not require a specific level of histocompatibility be present as part of the medical necessity evaluation).

Donor stem cells, either autologous or allogeneic, can be collected from either the bone marrow or the peripheral blood. Stem cells may be harvested from the peripheral blood using a pheresis procedure. To increase the number of stem cells in the peripheral circulation, donors may be pretreated with a course of chemotherapy or hematopoietic growth factors, or both.

In addition, blood harvested from the umbilical cord and placenta shortly after delivery of neonates contains stem and progenitor cells. Although cord blood is an allogeneic source, these stem cells are antigenically "naïve" and thus, are associated with a lower incidence of rejection or graft versus host disease.

The most appropriate stem cell source for a particular individual depends upon the disease, treatment history, and the availability of a compatible donor. The most appropriate source of stem cells for each individual must balance the risks of graft failure and re-infusion of malignant cells in autologous procedures, the risks of graft rejection, and graft versus host disease in allogeneic procedures.

While some HDC protocols can be administered on an outpatient basis, an inpatient stay may be required. Individuals receiving whole body radiotherapy, typically those receiving an allogeneic transplant might require prolonged hospitalization.

While the intensity of the regimens used for conditioning in conventional HDC varies, collectively they have been termed "myeloablative." Several less intense conditioning regimens have been developed recently and rely more on immunosuppression than cytotoxic effects to permit engraftment of donor cells. These regimens, collectively termed "non-myeloablative", also vary in intensity with substantial overlap between the ranges for "myeloablative" and "non-myeloablative" regimens. Studies have shown that donor allogeneic stem cells can engraft in recipients using less-intensive conditioning regimens that are sufficiently immunosuppressive to permit graft-host tolerance. This manifests as a stable mixed donor-host hematopoietic chimerism. Once chimerism has developed, a further infusion of donor leukocytes may be given to eradicate malignant cells by inducing a graft vs. tumor effect. Non-myeloablative allogeneic transplants also referred to as "mini-transplant" or "reduced intensity conditioning transplant (RIC)", are thought to be potentially as effective as conventional HDC followed by an allogeneic stem cell transplantation (AlloSCT), but with decreased morbidity and mortality related to the less intense non-myeloablative chemotherapy conditioning regimen. Consequently, for individuals with malignancies who are eligible for conventional HDC/AlloSCT, conditioning with milder, non-myeloablative regimens (NM-AlloSCT) represents a technical modification of an established procedure.

Tandem high-dose or non-myeloablative chemotherapy with autologous and/or allogeneic stem cell support is the planned administration of two cycles of high-dose chemotherapy, alone or with total body irradiation, each of which is followed by re-infusion of stem cells. Despite treatment with high-dose chemotherapy, many individuals with advanced malignancies eventually relapse, indicating the presence of residual neoplastic cells. The hypothesis is that eradication of residual tumor cells can be achieved using

multiple cycles of myeloablative or non-myeloablative chemotherapy with stem cell support.

Definitions

Ablative: Very high dose of a treatment, calculated to kill a tumor.

ABVD: A chemotherapy regimen consisting of the following agents:

Doxorubicin 25mg/m^2 IV on days 1, 15

Bleomycin 10mg/m^2 IV on days 1, 15

Vinblastine 6mg/m^2 IV on days 1, 15

Dacarbazine 375mg/m^2 on days 1, 15
Repeat cycle every 28 days. Generally given for 4 cycles.

Ann Arbor staging system: The Ann Arbor staging system is commonly used for individuals with NHL.

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 2 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 nodes with or without other lymph node regions on the same side of the diaphragm (IIE).
Stage III: involvement of lymph node regions on both sides of the diaphragm (III) that may also be accompanied by localized involvement of an extralymphatic organ or site (IIIE), by involvement of the spleen (IIIS), or both (IIIS+E).
StageIV: disseminated (multifocal) involvement of 1 or more extralymphatic sites with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement.

Bone marrow: A spongy tissue located within flat bones, including the hip and breast bones and the skull; this tissue contains stem cells, the precursors of platelets, red blood cells, and white cells.

Chemotherapy: Medical treatment of a disease, particularly cancer, with drugs or other chemicals.

Chimerism: Cell populations derived from different individuals. Chimerism may be mixed or complete.

Complete response/remission (CR): The disappearance of all signs of cancer in response to treatment. This does not always mean the cancer has been cured. Also called a complete response.

Cytotoxic: Treatment that is destructive to cells.

Eastern Cooperative Oncology Group (ECOG): One of the cooperative groups that work with the National Cancer Institute to identify important questions in cancer research and to design carefully controlled clinical trials.

ECOG Performance Status: A scale used to determine the individual's level of functioning.

0= Fully active, able to carry on all pre-disease performance without restriction
1= Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2= Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3= Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4= Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5= Dead

Failure to engraft: When the bone marrow infused during a bone marrow transplant does not take or is not accepted by the recipient.

Graft versus host disease: A life-threatening complication of bone marrow transplants in which the donated marrow causes an immune reaction against the recipient's body.

Hematopoietic stem cells: Primitive cells capable of replication and formation into mature blood cells in order to repopulate the bone marrow.

High-dose or myeloablative chemotherapy (HDC): The administration of cytotoxic agents using doses several times greater than the standard therapeutic dose.

HLA (human leukocyte antigen): A group of protein molecules located on bone marrow cells that can provoke an immune response.

Karnofsky Score: A measure of the individual's overall physical health, judged by their level of activity. The score is based on the following scale:

100%	Normal, no complaints, no signs of disease
90%	Capable of normal activity, few symptoms or signs of disease
80%	Normal activity with some difficulty, some symptoms or signs
70%	Caring for self, not capable of normal activity or work
60%	Requiring some help; can take care of most personal requirements
50%	Requires help often, requires frequent medical care
40%	Disabled, requires special care and help
30%	Severely disabled, hospital admission indicated but no risk of death
20%	Very ill, urgently requiring admission, requires supportive measures or treatment
10%	Moribund, rapidly progressive fatal disease processes
0%	Death

Lansky Score: A measure of the individual's overall physical health, judged by their level of activity; the score uses the following scale:

100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both greater restriction of and less time spent in play activity
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed but lies around much of the day, no active play but able to participate in all quiet play and activities
40	Mostly in bed; participates in quiet activities

30 In bed; needs assistance even for quiet play
20 Often sleeping; play entirely limited to very passive activities
10 No play; does not get out of bed
0 Unresponsive

Non-myeloablative chemotherapy: Less intense chemotherapy conditioning regimens, which rely more on immunosuppression than cytotoxic effects to permit engraftment of donor cells.

Partial response: A decrease in the size of a tumor or in the extent of cancer in the body, in response to treatment. May also called partial remission.

Post-transplant lymphoproliferative disorders (PTLDs): A heterogeneous group of lymphoid neoplasms associated with immunosuppression subsequent to solid organ transplantation (SOT) or allogeneic hematopoietic stem cell transplantation (HCT) (NCCN CNS Cancers, 2023)

Primary graft failure: When the bone marrow infused during a bone marrow transplant does not take or is not accepted by the recipient.

Primary refractory disease: Cancer that does not respond at the beginning of treatment. May also be called resistant disease.

Relapse: After a period of improvement, the signs and symptoms of cancer return.

Stanford V: A chemotherapy regimen consisting of the following agents:

Doxorubicin 25mg/m^2 IV/d on days 1, 15
Vinblastine[(a)] 6 mg/m^2/d IV on days 1, 15
Mechlorethamine 6 mg/m^2 IV on day 1
Vincristine[(a)] 1.4mg/m^2/d on days 8, 22
Bleomycin 5 units/m^2/d IV on days 6, 22
Etoposide 60 mg/m^2/d IV on days 15, 16
Prednisone[(b)] mg/m^2 PO qod

[(a)] For individuals greater than or equal to 50 years old, decrease dose to 4 mg/m^2 and 1 mg/m^2 for vinblastine and vincristine, respectively during cycle 3.
[(b)] Tapered by 10 mg qod starting week 10.

Repeat cycle every 28 days for 3 cycles

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT

38204	Management of recipient hematopoietic progenitor cell donor search and cell acquisition
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207-38215	Transplant preparation of hematopoietic progenitor cells [includes codes 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215]
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
38243	Hematopoietic progenitor cell (HPC); HPC boost

HCPCS

S2142	Cord blood-derived stem cell transplantation, allogeneic
S2150	Bone marrow or blood-derived peripheral stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage, marrow ablative therapy, drugs, supplies, hospitalization with outpatient follow-up, medical/surgical, diagnostic, emergency, and rehabilitative services, and the number of days of pre- and post-transplant care in the global definition

ICD-10 Procedure

	Autologous transplantation
30233G0-30243G0	Transfusion of autologous bone marrow into peripheral or central vein, percutaneous approach [includes codes 30233G0, 30243G0]
30233Y0-30243Y0	Transfusion of autologous hematopoietic stem cells into peripheral or central vein, percutaneous approach [includes codes 30233Y0, 30243Y0]
	Allogeneic transplantation
30233G2-30243G4	Transfusion of allogeneic bone marrow, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233G2, 30233G3, 30233G4, 30243G2, 30243G3, 30243G4]
30233U2-30243U4	Transfusion of allogeneic T-cell depleted hematopoietic stem cells, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233U2, 30233U3, 30233U4, 30243U2, 30243U3, 30243U4]

30233X2-30243X4	Transfusion of allogeneic cord blood stem cells, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233X2, 30233X3, 30233X4, 30243X2, 30243X3, 30243X4]
30233Y2-30243Y4	Transfusion of allogeneic hematopoietic stem cells, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233Y2, 30233Y3, 30233Y4, 30243Y2, 30243Y3, 30243Y4]
	Pheresis [autologous or allogeneic]
6A550ZV	Pheresis of hematopoietic stem cells, single
6A551ZV	Pheresis of hematopoietic stem cells, multiple

ICD-10 Diagnosis

C81.00- C81.99	Hodgkin lymphoma
C82.00-C85.99	Follicular, non-follicular, mature T/NK-cell, and other specified and unspecified types of non-Hodgkin lymphoma
C86.0-C86.6	Other specified types of T/NK-cell lymphoma
C91.50-C91.52	Adult T-cell lymphoma/leukemia (HTLV-1-associated)

When services are Investigational and Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

References

Peer Reviewed Publications:

1. Al Khabori, de Almeida JR, Guyatt GH, et al. Autologous stem cell transplantation in follicular lymphoma: a systematic review and meta-analysis. J Natl Cancer Inst. 2012; 104(1):18-28.
2. Anagnostopoulos A, Giralt S. Critical review on non-myeloablative stem cell transplantation (NST). Crit Rev Oncol Hematol. 2002; 44(2):175-190.
3. Berdeja JG, Jones RJ, Zahurak ML, et al. Allogeneic bone marrow transplantation in patients with sensitive low-grade lymphoma or mantle cell lymphoma. Biol Blood Marrow Transplant. 2001; 7(10):561-567.
4. Bolwell B, Kalaycio M, Andresen S, et al. Autologous peripheral blood progenitor cell transplantation for transformed diffuse large-cell lymphoma. Clin Lymphoma. 2000; 1(3):226-231; discussion 232-233.
5. Buske C, Hoster E, Dreyling M, et al. The Follicular Lymphoma International Prognostic Index (FLIPI) separates high-risk from intermediate- or low-risk patients with advanced-stage follicular lymphoma treated front-line with rituximab and the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with respect to treatment outcome. Blood. 2006; 108(5):1504-1508.
6. Chan KW, Grimley MS, Taylor C, Wall DA. Early identification and management of graft failure after unrelated cord blood transplantation. Bone Marrow Transplant. 2008; 42(1):35-41.
7. Chen CI, Crump M, Tsang R, et al. Autotransplants for histologically transformed follicular non-Hodgkin's lymphoma. Br J Haematol. 2001; 113(1):202-208.
8. Corradini P, Tarella C, Olivieri A, et al. Reduced-intensity conditioning followed by allografting of hematopoietic cells can produce clinical and molecular remissions in patients with poor-risk hematologic malignancies. Blood. 2002; 99(1):75-82.
9. Dada R, Usman B. Allogeneic hematopoietic stem cell transplantation in r/r Hodgkin lymphoma after treatment with checkpoint inhibitors: Feasibility and safety. Eur J Haematol. 2019; 102(2):150-156.
10. Damon LE, Johnson JL, Niedzwiecki D, et al. Immunochemotherapy and autologous stem-cell transplantation for untreated patients with mantle-cell lymphoma: CALGB 59909. J Clin Oncol. 2009; 27(36):6101-6108.
11. Dimopoulos MA, Gertz MA, Kastritis E, et al. Update on treatment recommendations from the Fourth International Workshop on Waldenström's Macroglobulinemia. J Clin Oncol. 2009; 27(1):120-126.
12. Djulbegovic B, Seidenfeld J, Bonnell C, Kumar A. Nonmyeloablative allogeneic stem-cell transplantation for hematologic malignancies: a systematic review. Cancer Control. 2003; 10(1):17-41.
13. Federico M, Bellei M, Marcheselli L, et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. J Clin Oncol. 2009; 27(27):4555-4562.
14. 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; 20(2):467-475.
15. Georges GE, Maris M, Sandmaier BM, et al. Related and unrelated nonmyeloablative hematopoietic stem cell transplantation for malignant disease. Int J Hematol. 2002; 76 Suppl 1:184-189.
16. Giralt S. Update on non-myeloablative stem cell transplantation for hematologic malignancies. Int J Hematol. 2002; 76 Suppl 1;176-183.
17. Giralt S, Thall PF, Khouri I, et al. Melphalan and purine analog-containing preparative regimens: reduced-intensity conditioning for patients with hematologic malignancies undergoing allogeneic progenitor cell transplantation. Blood. 2001; 97(3):631-637.
18. Gopal AK, Rajendran JG, Petersdorf SH, et al. High-dose chemo-radioimmunotherapy with autologous stem cell support for relapsed mantle cell lymphoma. Blood. 2002; 99(9):3158-3162.
19. Greb A, Bohlius J, Trelle S, et al. High-dose chemotherapy with autologous stem cell support in first-line treatment of aggressive non-Hodgkin lymphoma – results of a comprehensive meta-analysis. Cancer Treat Rev. 2007; 33(4):338-346.
20. Hahn T, Wolff SN, Czuczman M, et al. ASBMT Expert Panel. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of diffuse large cell B-cell non-Hodgkin's lymphoma: an evidence-based review. Biol Blood and Marrow Transpl. 2001; 7(6):308-331.
21. Haioun C, Mounier N, Quesnel B, et al. Tandem autotransplants as first-line consolidative treatment in poor-risk aggressive lymphoma: a pilot study of 36 patients. Ann Oncol. 2001; 12(12):1749-1755.
22. Larocca A, Piaggio G, Podestà M, et al. Boost of CD34+-selected peripheral blood cells without further conditioning in patients with poor graft function following allogeneic stem cell transplantation. Haematologica. 2006; 91(7):935-940.
23. McSweeney PA, Niederwieser D, Shizuru JA, et al. Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. Blood. 2001; 97(11):3390-3400.
24. Milpied N, Deconinck E, Gaillard F, et al. Initial treatment of aggressive lymphoma with high dose chemotherapy and autologous stem-cell support. N Engl J Med. 2004; 350(13):1287-1295.
25. 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; 26(36):5980-5987.

26. Moskowitz AJ, Perales MA, Kewalramani T, et al. Outcomes for patients who fail high dose chemoradiotherapy and autologous stem cell rescue for relapsed and primary refractory Hodgkin lymphoma. Br J Haematol. 2009; 146(2):158-163.
27. Okamoto S. Current indications of hematopoietic cell transplantation in adults. Hematol Oncol Stem Cell Ther. 2017; 10(4):178-183.
28. Oliansky DM, Gordon LI, King J, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of follicular lymphoma: an evidence-based review. Biol Blood Marrow Transplant. 2010; 16(4):443-468.
29. Ostrom QT, Price M, Neff C, et al. CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2015-2019. Neuro Oncol. 2022; 24(Suppl 5):v1-v95.
30. Papadopoulos KP, Noguera-Irizarry W, Hesdorffer CS. Tandem transplantation in lymphoma. Bone Marrow Transplant. 2001; 28(6):529-535.
31. Rapoport AP, Meisenberg B, Sarkodee-Adoo C, et al. Autotransplantation for advanced lymphoma and Hodgkin's disease followed by post-transplant rituxan/GM-CSF or radiotherapy and consolidation chemotherapy. Bone Marrow Transplant. 2002; 29(4):303-312.
32. 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; 31(1):27-32.
33. 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; 14(8):904-912.
34. Solal-Céligny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood. 2004; 104(5):1258-1265.
35. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005; 106(8):2912-2919.
36. Tam CS, Bassett R, Ledesma C, et al. Mature results of the M.D. Anderson Cancer Center risk-adapted transplantation strategy in mantle cell lymphoma. Blood. 2009; 113:4144-4152.
37. Vigouroux S, Michallet M, Porcher R, et al. Long-term outcomes after reduced-intensity conditioning allogeneic stem cell transplantation for low-grade lymphoma: a survey by the French Society of Bone Marrow Graft Transplantation and Cellular Therapy (SFGM-TC). Haematologica. 2007; 92(5):627-634.
38. Villela L, Sureda A, Canals C, et al. Low transplant-related mortality in older patients with hematologic malignancies undergoing autologous stem cell transplantation. Haematologica. 2003; 88(3):300-305.
39. Vose JM. Mantle cell lymphoma: 2012 update on diagnosis, risk-stratification, and clinical management. Am J Hematol. 2012; 87(6):604-609.
40. Williams CD, Harrison CN, Lister TA, et al. High-dose therapy and autologous stem-cell support for chemosensitive transformed low-grade follicular non-Hodgkin's lymphoma: a case-matched study from the European Bone Marrow Transplant Registry. J Clin Oncol. 2001; 19(3):727-735.

Government Agency, Medical Society, and Other Authoritative Publications:

1. American Society for Transplantation and Cellular Therapy. Policy Statements, Guidelines and Reviews. Available at: https://www.astct.org/advocate/policy-statements. Accessed on January 16, 2023.
    - Follicular Lymphoma. Updated 2011.
    - Diffuse Large Cell B Lymphoma. Updated 2011.
2. Centers for Medicare and Medicaid Services. National Coverage Determination Stem Cell Transplantation. NCD #110.23. Effective January 27, 2016. Available at: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=366&ncdver=1&bc=AgAAQAAAAAAA&. Accessed on January 19, 2024.
3. Greb A, Bohlius J, Schiefer D, et al. High-dose chemotherapy with autologous stem cell transplantation in the first line treatment of aggressive non-Hodgkin lymphoma (NHL) in adults. Cochrane Database Syst Rev. 2008; (1):CD004024.
4. International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med. 1993 Sep 30;329(14):987-994.
5. Kyriakou C, Canals C, Sibon D, et al. High-dose therapy and autologous stem-cell transplantation in Waldenstrom Macroglobulinemia: The Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol. 2010; 28(13):2227-2232.
6. 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; 21(11):1863-1869.
7. Munshi PN, Hamadani M, Kumar A, et al. American Society of Transplantation and Cellular Therapy, Center of International Blood and Marrow Transplant Research, and European Society for Blood and Marrow Transplantation clinical practice recommendations for transplantation and cellular therapies in mantle cell lymphoma. Transplant Cell Ther. 2021; 27(9):720-728.
8. NCCN Clinical Practice Guidelines in Oncology™: © 2024 National Comprehensive Cancer network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on January 19, 2024.
    - B-Cell Lymphomas (V.1.2024). Revised January 18, 2024.
    - Central Nervous System Cancers (V1.2023). Revised March 24, 2023.
    - Hairy Cell Leukemia (V.1.2024). Revised November 3, 2023.
    - Hodgkin Lymphoma (V.1.2024). Revised October 12, 2023.
    - Primary Cutaneous Lymphomas. (V.1.2024). Revised December 21, 2023.
    - T-Cell Lymphomas (V.1.2024). Revised December 21, 2023.
    - Waldenström's macroglobulinemia/Lymphoplasmacytic lymphoma (V.2.2024). Revised December 5, 2023.
9. Rancea M, Monsef I, von Tresckow B, et al. High-dose chemotherapy followed by autologous stem cell transplantation for patients with relapsed/refractory Hodgkin lymphoma. Cochrane Database Syst Rev. 2013; (6):CD009411.
10. Schaaf M, Reiser M, Borchmann P, et al. High-dose therapy with autologous stem cell transplantation versus chemotherapy or immuno-chemotherapy for follicular lymphoma in adults. Cochrane Database Syst Rev. 2012; (1):CD007678.
11. Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984-87). Br J Haematol. 1991; 79(3):428-437.

Websites for Additional Information

1. American Cancer Society. Lymphoma. Available at: Lymphoma Cancer | Understanding Lymphoma | American Cancer Society. Accessed on January 19, 2024.
2. National Cancer Institute. Lymphoma. Available at: http://www.cancer.gov/cancertopics/types/alphalist. Accessed on January 19, 2024.
3. National Cancer Institute. Bone Marrow Transplantation and Peripheral Blood Stem Cell Transplantation: Questions and Answers. Updated on October 5, 2023. Available at: http://www.cancer.gov/cancertopics/factsheet/Therapy/bone-marrow-transplant. Accessed on January 19, 2024.

Index

Document History

Status	**Date**	**Action**
Revised	02/15/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated formatting in Position Statement section. In the med nec Position Statement section for NHL, created criterion B3. In the INV/NMN section for NHL, updated bullet “A” by adding “when criteria above are not met, including”. Updated Rationale, Background/Overview, References and Websites for Additional Information sections. Updated Coding section to add ICD-10-CM codes C91.50-C91.52.
Reviewed	02/16/2023	MPTAC review. Updated Rationale, Discussion, References and Websites for Additional Information sections.
Reviewed	02/17/2022	MPTAC review. Updated Rationale, Discussion, References and Websites sections.
	10/01/2021	Updated Coding section with 10/01/2021 ICD-10-PCS changes; removed open approach codes deleted 09/30/2021.
Reviewed	02/11/2021	MPTAC review. Updated Rationale, Discussion, References and Websites sections.
Reviewed	02/20/2020	MPTAC review. Updated Rationale, Discussion, References and Websites sections.
	10/01/2019	Updated Coding section with 10/01/2019 ICD-10-PCS changes; added 30230U2-30243U4; removed 30250G0-30263G1, 30250X1-30263Y1 deleted 09/30/2019.
Reviewed	03/21/2019	MPTAC review.
Reviewed	03/20/2019	Hematology/Oncology Subcommittee review. Updated Rationale, Background, References and Websites sections.
Reviewed	07/26/2018	MPTAC review.
Reviewed	07/18/2018	Hematology/Oncology Subcommittee review. Updated Rationale, Background, References and Websites sections.
Revised	11/02/2017	MPTAC review.
Revised	11/01/2017	Hematology/Oncology Subcommittee review. The document header wording updated from “Current Effective Date” to “Publish Date”. In the Position Statement, removed the requirement that individuals must meet the “Individual Selection Criteria for all diagnoses” Updated Rationale, Background, References and Websites sections.
Reviewed	11/03/2016	MPTAC review.
Reviewed	11/02/2016	Hematology/Oncology Subcommittee review. Updated formatting in position statement. Updated Rationale, Background, References and Websites sections.
	10/01/2016	Updated Coding section with 10/01/2016 ICD-10-PCS procedure code changes.
Reviewed	11/05/2015	MPTAC review.
Reviewed	11/04/2015	Hematology/Oncology Subcommittee review. Updated Rationale, Background, References and Websites sections. Removed ICD-9 codes from Coding section.
Reviewed	11/13/2014	MPTAC review.
Reviewed	11/12/2014	Hematology/Oncology Subcommittee review. Updated Description, References, Websites and Index section.
Reviewed	11/14/2013	MPTAC review.
Reviewed	11/13/2013	Hematology/Oncology Subcommittee review. Updated Rationale, References and Websites.
Revised	11/08/2012	MPTAC review.
Revised	11/07/2012	Hematology/Oncology Subcommittee review. Added note defining tandem transplantation to the Position Statement Section. Added medically necessary indication for autologous stem cell transplantation for mantle cell lymphoma to consolidate a first CR. Updated Rationale, References and Websites. Updated Coding section with 01/01/2013 CPT changes.
Revised	11/17/2011	MPTAC review.
Revised	11/16/2011	Hematology/Oncology Subcommittee review. Clarified stem cell harvest criteria for NHL. Updated Rationale, References and Websites. Updated Coding section with 01/01/2012 CPT changes.
Revised	11/18/2010	MPTAC review.
Revised	11/17/2010	Hematology/Oncology Subcommittee review. Modified Position Statements to clarify indications and for formatting consistency. Added medically necessary indication for tandem autologous stem cell transplantation to treat Hodgkin Disease when criteria are met. Modified tandem investigational and not medically necessary statement. Updated Rationale, References and Websites.
Revised	02/25/2010	MPTAC review. Added criteria to medically necessary stem cell harvest language.
Revised	11/19/2009	MPTAC review.
Revised	11/18/2009	Hematology/Oncology Subcommittee review. Clarified medically necessary stem cell harvest language for anticipated but unscheduled transplant.
Revised	05/21/2009	MPTAC review.
Revised	05/20/2009	Hematology/Oncology Subcommittee review. Deleted medically necessary criteria for prophylactic harvest and storage for Hodgkin disease. Clarified harvest and storage for follicular NHL. Updated rationale to include information about stem cell “boosts”. Background, references and websites updated.
Reviewed	11/20/2008	MPTAC review.

Reviewed	11/19/2008	Hematology/Oncology Subcommittee review. Updated rationale, background, references and websites. Clarified Patient Selection Criteria. Separated investigational and not medically necessary statements for autologous and allogeneic tandem transplants.
	01/01/2008	Updated Coding section with 01/01/2008 HCPCS changes; removed HCPCS G0267 deleted 12/31/2007.
Revised	11/29/2007	MPTAC review.
Revised	11/28/2007	Hematology/Oncology Subcommittee review. Moved classification information from the medically necessary section into the Rationale section. Updated references, websites. The phrase “investigational/not medically necessary” was clarified to read “investigational and not medically necessary.”
	05/17/2007	Added note to cross reference TRANS.00016 Umbilical Cord Blood Progenitor Cell Collection, Storage and Transplantation.
Revised	12/07/2006	MPTAC review.
Revised	12/06/2006	Hematology/Oncology Subcommittee review. Revision of harvest and storage language for Hodgkin’s lymphoma. Addition of graft failure indication.
Revised	06/08/2006	MPTAC review.
Revised	06/07/2006	Hematology/Oncology Subcommittee review. Revision to general patient selection criteria.
Revised	12/01/2005	MPTAC review.
Revised	11/30/2005	Hematology/Oncology Subcommittee review. Eliminated age requirements and revised general patient selection criteria.
	11/22/2005	Added reference for Centers for Medicare and Medicaid Services (CMS) – National Coverage Determination (NCD).
Reviewed	07/14/2005	MPTAC review.
Revised	04/28/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organization	**Last Review Date**	**Document Number**	**Title**
Anthem, Inc.	10/28/2004	TRANS.00002	Stem Cell Transplant following Chemotherapy for Malignant Diseases
WellPoint Health Networks, Inc.	12/02/2004	7.11.02	Autologous Bone Marrow Transplantation or Peripheral Blood Stem Cell Support (PBSCS) for Malignancies
	12/02/2004	7.11.03	Allogeneic Bone Marrow or Stem Cell Transplantation
	12/02/2004	7.11.05	Mini-Transplants
	12/02/2004	Clinical Guideline	Bone Marrow Transplant for Hodgkin’s Disease
	12/02/2004	Clinical Guideline	Bone Marrow Transplant for non-Hodgkin’s Lymphoma
	12/02/2004	Clinical Guideline	Second Bone Marrow/Stem Cell Treatment

---

Applicable to Commercial HMO members in California: When a medical policy states a procedure or treatment is investigational, PMGs should not approve or deny the request. Instead, please fax the request to Anthem Blue Cross Grievance and Appeals at fax # 818-234-2767 or 818-234-3824. For questions, call G&A at 1-800-365-0609 and ask to speak with the Investigational Review Nurse.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member’s contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.