Clinical Policy Bulletin:  
Hematopoietic Cell Transplantation for Non-Hodgkin's Lymphoma

Number: 0494

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

I. Autologous Hematopoietic Cell Transplantation

Aetna considers autologous hematopoietic cell transplantation for the treatment of persons with relapsed or primary refractory (see "Note" below) non-Hodgkin's lymphoma (NHL) medically necessary if the person meets the transplanting institution's protocol eligibility criteria. In the absence of a protocol, Aetna considers autologous hematopoietic cell transplantation medically necessary for the treatment of NHL when all of the following selection criteria are met:

A. Person has relapsed or refractory NHL.  *Note: Upon clinical review, Aetna may also consider autologous hematopoietic cell transplantation medically necessary for persons in first clinical remission with lymphoblastic NHL, Burkitt’s lymphoma, mediastinal B-cell lymphoma, mantle cell lymphoma, high-risk diffuse large B-cell lymphoma and other NHLs that are associated with poor prognosis.

and

B. Evidence of chemotherapy responsive (see note below) disease.*

*Note: Upon medical review, autologous hematopoietic cell transplantation may be considered medically necessary for persons with chemoresistant disease where disease is relapsed and widely metastatic and allogeneic transplantation can not be offered.

and

C. No evidence of serious organ dysfunction based upon the transplanting institution's evaluation.

Notes:

Responsiveness is defined as a tumor demonstrating either a complete or partial remission. Partial remission (response) is defined as at least a 50% decrease in tumor burden.

Refractory disease is a failure to attain a complete or partial response. The refractoriness can be primary (failure to respond to initial therapy) or secondary (initial response but failure to respond after disease relapse).
Aetna considers autologous hematopoietic cell transplantation experimental and investigational for persons with any of the following contraindications to autologous hematopoietic cell transplantation for the treatment of NHL:

A. Co-morbid diseases (e.g., uncontrolled hypertension)
B. Evidence of serious organ dysfunction.

II. Allogeneic Hematopoietic Cell Transplantation

Aetna considers allogeneic hematopoietic cell transplantation medically necessary for the treatment of persons with relapsed NHL (including persons who have relapsed after autologous hematopoietic cell transplantation) or primary refractory (see "Note" below) NHL (low-grade, intermediate-grade, and high-grade) if the person meets the transplanting institution's protocol eligibility criteria. In the absence of a protocol, all of the following medical necessity criteria must be met:

A. Person has relapsed or refractory NHL. *Note: Upon clinical review, Aetna may also consider allogeneic hematopoietic cell transplantation medically necessary for persons in first clinical remission with lymphoblastic NHL, Burkitt's lymphoma, mediastinal B-cell lymphoma, mantle cell lymphoma and other NHLs that are associated with poor prognosis.
B. Person has a haploidalientical to fully HLA-matched related donor or well-matched unrelated donor (i.e., meets National Marrow Donor Program (NMDP) criteria for selecting unrelated donors) or single or double cord blood matched for at least 4 of 6 HLA ABDR antigens; and
C. No serious organ dysfunction based upon the transplanting institution's evaluation.

Notes:

Aetna considers non-myeloablative allogeneic hematopoietic cell transplantation medically necessary ("mini-transplant", reduced intensity conditioning transplant) for the treatment of persons with relapsed NHL (including persons who have relapsed after ABMT) or primary refractory (see note below) NHL (low-grade, intermediate-grade, and high-grade) when they are eligible for conventional allografting or a reduced intensity regimen is preferred by the transplant center.

Tandem Transplant

Aetna considers tandem autologous hematopoietic cell transplantation (auto-auto) or tandem autologous hematopoietic cell transplantation followed by allogenic hematopoietic cell transplantation (auto-allo) experimental and investigational for NHL due to a lack of adequate evidence in the peer-reviewed published medical literature of their safety and effectiveness.

Background

Non-Hodgkin's lymphoma (NHL) is an extremely heterogeneous group of lymphoid malignancies whose diversity relates to their epidemiology, natural history, morphology, immunology, cytogenetics and response to standard doses of chemotherapy.

There have been various attempts at classification schemes for NHL resulting in confusing and overlapping terminology in the literature. Historically, the most common scheme has been the Rappaport classification, which subdivided lymphomas based on their resemblance to normal appearing lymphocytes. In 1982, this classification scheme was supplanted in the literature by a National Cancer Institute Working Formulation (IWF), which was an attempt at providing a common language for classification. The following table summarizes the two systems.
Rappaport and International Working Formulation Classification of Lymphomas:

<table>
<thead>
<tr>
<th>Rappaport System</th>
<th>Grade/Histologic Type (IWF Class)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Grade</td>
<td></td>
</tr>
<tr>
<td>Diffuse, well differentiated</td>
<td>Small lymphocytic (A)</td>
</tr>
<tr>
<td>Nodular poorly differentiated</td>
<td>Predominantly small-cleaved cell, follicular; diffuse areas, sclerosis (B)</td>
</tr>
<tr>
<td>Nodular, mixed histiocytic and lymphocytic</td>
<td>Mixed, small-cleaved and large-cell, follicular; diffuse areas (C)</td>
</tr>
<tr>
<td>Intermediate Grade</td>
<td></td>
</tr>
<tr>
<td>Nodular histiocytic</td>
<td>Predominantly large-cell, follicular; diffuse areas, sclerosis (D)</td>
</tr>
<tr>
<td>Diffuse, poorly differentiated lymphocytic</td>
<td>Small-cleaved cell, diffuse (E)</td>
</tr>
<tr>
<td>Diffuse mixed histiocytic and lymphocytic</td>
<td>Mixed small and large-cell, diffuse; sclerosis, epithelioid cell component (F)</td>
</tr>
<tr>
<td>Diffuse histiocytic</td>
<td>Large-cell cleaved or non-cleaved, diffuse; sclerosis (G)</td>
</tr>
<tr>
<td>High Grade</td>
<td></td>
</tr>
<tr>
<td>Diffuse histiocytic</td>
<td>Large-cell, immunoblastic; plasmacytoid, epithelioid cell component (H)</td>
</tr>
<tr>
<td>Lymphoblastic</td>
<td>Lymphoblastic, convoluted or non-convoluted cell (I)</td>
</tr>
<tr>
<td>Diffuse, undifferentiated, Burkitt and non-Burkitt</td>
<td>Small non-cleaved cell (J)</td>
</tr>
</tbody>
</table>

Lymphomas are often typically staged according to the extent of their dissemination. The Ann Arbor Staging System, specifically developed for Hodgkin's disease, has been adapted for use in lymphomas.

**Ann Arbor Staging System for Lymphomas:**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement of a single lymph node region (I) or a single extra-lymphatic organ or site (IE)</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extra-lymphatic organ or site (IIIE). An optional recommendation is that the numbers of node regions involved be indicated by a subscript (i.e., II3)</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph node regions on both sides of the diaphragm (III) or localized involvement of an extra-lymphatic organ or site (IIIE) or spleen (IIIS) or both (IIISE)</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse or disseminated involvement of 1 or more extra-lymphatic organs or tissues with or without associated lymph node involvement. The reason for classifying the patient as Stage IV should be identified further be defining site by symbols</td>
</tr>
</tbody>
</table>

Stages I, II, III, and IV can be sub-classified into A or B category. Category “B” is for patients with well-defined, generalized symptoms such as unexplained fever (temperature greater than 38°C), drenching night sweats, and unexplained weight loss of more than 10% of body weight in the 6 months prior to
diagnosis, while category “A” is for patients without these symptoms.

In 1994, the Revised European-American Classification of Lymphoid Neoplasms (REAL) was constructed to define a particular NHL by incorporating all available tumor information-morphologic, immunotypic, genetic, and clinical features. A project to update and revise the REAL system was initiated by the World Health Organization (WHO) in 1995; its consensus was published in 1999. The WHO classification, like REAL, incorporates a number of tumor characteristics and is designed to enable disease identification by pathologic examination while maintaining clinical relevance. With use of the WHO classification, treatment is determined by identifying the specific lymphoma type and, if relevant, by considering tumor grade and other prognostic factors.

REAL/WHO Classification System:

<table>
<thead>
<tr>
<th>Indolent</th>
<th>B-cell CLL/small lymphocytic lymphoma</th>
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<tbody>
<tr>
<td>Marginal zone lymphoma</td>
<td></td>
</tr>
<tr>
<td>■ MALT</td>
<td></td>
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<tr>
<td>■ Splenic marginal zone lymphoma</td>
<td></td>
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<tr>
<td>■ Nodal marginal zone lymphoma</td>
<td></td>
</tr>
<tr>
<td>Lymphoplasmacytoid lymphoma/immunocytoma</td>
<td></td>
</tr>
<tr>
<td>Follicle center lymphoma, follicular type</td>
<td></td>
</tr>
<tr>
<td>■ Grade 1 (0 - 5 centroblasts/hpf)</td>
<td></td>
</tr>
<tr>
<td>■ Grade 2 (6 - 15 centroblasts/hpf)</td>
<td></td>
</tr>
<tr>
<td>■ Grade 3† (greater than 15 centroblasts/hpf)</td>
<td></td>
</tr>
<tr>
<td>Aggressive</td>
<td></td>
</tr>
<tr>
<td>Diffuse, large cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>■ Mediastinal large cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>■ Primary effusion lymphoma</td>
<td></td>
</tr>
<tr>
<td>Mantle cell lymphoma†</td>
<td></td>
</tr>
<tr>
<td>Burkitt's lymphoma/high-grade Burkitt's like</td>
<td></td>
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<tr>
<td>Precursor B-cell leukemia/lymphoma</td>
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</table>

Key: CLL = chronic lymphocytic leukemia; MALT = mucosa-associated lymphoid tissue; hpf = high-powered field.

† Subtype may exhibit either indolent or aggressive clinical behavior.

A staging system of the extent of disease is only useful if it reflects a patient's prognosis and can be used to select appropriate therapy. The Ann Arbor Staging System is based on the pattern of contiguous nodal spread that is typically observed in Hodgkin's disease and it is assumed that a higher stage is associated with a worse prognosis. However, in indolent lymphomas, the majority of patients present with disseminated disease that would be classified as Stage IV and except for the rare patient who truly has Stage I disease, there is little difference in prognosis among the other stages. In addition, the Ann Arbor System gives no consideration to tumor size, which is prognostically significant in
lymphomas. Furthermore, the diaphragm is an arbitrary anatomic reference point, dictated by convenience and by the standard size of radiation fields. Thus, Stage II disease represents an extremely heterogeneous group of patients, who may have from 2 to 12 sites of involvement. They will all be classified as Stage II if their disease is located entirely on one side of the diaphragm. Similarly, Stage II could include patients with isolated disease on both sides of the diaphragm, and patients with bulky widely disseminated disease. The following staging system proposed by the National Cancer Institute modifies the Ann Arbor Staging System in order to reflect the natural history of lymphomas and to provide more prognostically useful information.

**Modified Ann Arbor Staging System:**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Localized nodal or extra-nodal disease (Ann Arbor Stage I or IE)</td>
</tr>
<tr>
<td>II</td>
<td>Two or more nodal sites of disease or a localized extra-nodal site plus draining nodes with none of the following poor prognostic factors: performance status less than 70, Category B symptoms, any mass greater than 10 cm in diameter, serum lactate dehydrogenase greater than 500 U/L, 3 or more extra-nodal sites of disease</td>
</tr>
<tr>
<td>III</td>
<td>Stage II plus any poor prognostic features listed above</td>
</tr>
</tbody>
</table>

**High-Dose Chemotherapy**

High-dose chemotherapy (HDC) 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 most significant side effect of HDC is marrow ablation and thus HDC is accompanied by a re-infusion of hematopoietic stem cells in order to repopulate the bone marrow. The potential source of stem cells and harvesting techniques are described below.

High-dose chemotherapy bone marrow or peripheral stem cell transplant (autologous or allogeneic) is a treatment option for selected patients with NHL. The basic concept behind HDC is a combination regimen of marrow ablative drugs which have different mechanism of action to maximally eradicate the malignant cells, and non-overlapping toxicity such that the doses can be maximized as much as possible. Total body irradiation (TBI) is an additional variable. Patients with the disease who are responsive to standard doses of chemotherapy, and are either asymptomatic or have a good performance status and who do not have any serious co-morbidities are considered optimal candidates for HDC.

Autologous bone marrow transplant entails the patient acting as his/her own bone marrow donor. Stem cells may be harvested from the patient's bone marrow or more commonly, peripheral blood. Peripheral stem cells are harvested via 1 or morepheresis procedures. The patient's bone marrow is harvested via aspiration from the iliac crests under general or regional anesthesia. The marrow is then preserved and re-infused following completion of a potent chemotherapy regimen. This process provides pluripotent marrow stem cells to reconstitute (i.e., rescue) the patient's marrow from the myeloablative effects of high dose cytotoxic chemotherapeutic agents. A prior course of chemotherapy (typically cyclophosphamide) or growth factors or both can increase the number of circulating stem cells.

Autologous bone marrow transplant (ABMT) or peripheral stem cell transplant (ASCT) permits the use of chemotherapeutic agents at doses that exceed the myelotoxicity threshold; consequently, a greater tumor cell kill might be anticipated. It has been suggested that the resultant effect is greater response rate and possibly an increased cure rate.

Allogeneic bone marrow transplant refers to the use of functional hematopoietic stem cells from a healthy donor to restore bone marrow function following HDC. Allogeneic stem cells can be harvested
from either the bone marrow or peripheral blood. For patients with marrow-based malignancies, the use of allogeneic stem cells offers the advantage of lack of tumor cell contamination, particularly if the stem cells are harvested from the bone marrow, as opposed to from the peripheral blood. Furthermore, allogeneic stem cells may be associated with a potentially beneficial graft versus tumor effect.

Syngeneic stem cells refer to genetically identical bone marrow or peripheral stem cells harvested from an identical twin. Syngeneic cells can be harvested from either the bone marrow or peripheral blood.

Tandem (sequential) transplant protocols utilize a cycle of HDC with ASCT followed in approximately 6 months by a 2nd cycle of HDC and/or TBI with another ASCT. This is done in an attempt to obtain greater and extended response rates. To date, there have been no definitive studies showing that tandem transplants improve response rates, event-free survival or overall survival more than single transplants for patients with NHL. Ahmed et al (2005) reported that the median disease-free survival of patients with resistant/refractory NHL treated with tandem stem cell transplant was only 2 months.

Oliansky and colleagues (2011) presented clinical research published since the 2001 evidence-based review on the role of hematopoietic stem cell transplantation (HSCT) in the treatment of diffuse large B cell lymphoma (DLBCL) in adults. Treatment recommendations that remain unchanged from the original review include: (i) ASCT as salvage therapy is recommended for patients with chemo-sensitive relapsed DLBCL; and (ii) ASCT is not recommended for patients who achieve a partial response to an abbreviated induction regimen. New treatment recommendations based on new published data include: (i) ASCT as first-line therapy is not recommended for any international prognostic index (IPI) group; (ii) planned tandem or multiple sequential ASCT is not recommended; (iii) peripheral blood is the standard stem cell source for ASCT; (iv) age is not a contraindication for ASCT, although outcomes in older adults are not as good as in younger adults. There are insufficient data to make recommendations on the routine use of rituximab maintenance after ASCT, autologous versus allogeneic SCT, fewer versus more cycles of induction therapy prior to ASCT, or the use of reduced intensity versus myeloablative conditioning regimens.

Prior to HDC-ABMT, the literature indicates that patients generally undergo induction therapy with vincristine, doxorubicin and dexamethasone, melphalan and prednisone or other combination salvage regimens. Conventional dosages of these drugs can typically be given on an outpatient basis. Hospitalization may be required due to neutropenic fever, nausea and vomiting, mucositis, diarrhea, or inadequate oral intake.

Prior to peripheral stem cell collection, the literature states that an apheresis catheter may be inserted during an ambulatory surgical procedure. The apheresis catheter can be placed during the same anesthesia procedure if a bone marrow harvest is also planned. Apheresis is an outpatient procedure, which is done on a daily basis until adequate stem cells are collected. From 5 to 10 procedures may be necessary.

Stem cell mobilization, in which cyclophosphamide and/or GM-CSF are used to flush the critical stem cells from the bone marrow into the peripheral circulation, may also be part of the stem cell collection. Protocols vary -- some institutions administer intermediate doses of cyclophosphamide (4 g/m2) as an outpatient procedure, followed by apheresis in 5 to 14 days when the blood counts have recovered. When high-dose cyclophosphamide (6 g/m2) is used, a 4-day hospitalization is usually required for pre- and post-chemotherapy hydration. After completion of the cyclophosphamide regimen, the literature indicates that the patient can usually be discharged; apheresis can usually be administered on an outpatient basis once the acute period of bone marrow hypoplasia has resolved.

Hospitalization for the HDC component of the procedure depends on the regimen. High-dose melphalan (140 to 200 mg/m2) is typically given on an outpatient basis with home hydration therapy. Other high dose combination therapies, such as EDAP (etoposide, dexamethasone, ara-C and cisplatin) require hospitalization due to nausea and vomiting, mucositis, diarrhea and inadequate oral intake. Any regimen that includes TBI will require a prolonged hospital stay, typically lasting about 30 days. Patients receiving HDC with or without TBI are usually initially treated in a private room for about 1 week until the
blood counts start to drop. Then patients are typically transferred to a specialized laminar flow room for the duration of their hospital stay.

Usual length of stay for patients undergoing peripheral stem cell collection with high-dose cyclophosphamide mobilization is 4 days. Other stem cell mobilization protocols normally do not require a hospital stay.

Usual length of stay for patients hospitalized for complications related to HDC depend on resolution of fever (i.e. fever free for 48 hours while off all antibiotics), adequate blood counts (i.e., WBC greater than 500), and resolution of other morbidity such as mucositis and diarrhea. The patient must also be able to maintain adequate oral intake. Hospital stays typically range from 2 to 4 weeks. Patients may be discharged even if they require transfusions to maintain an adequate platelet count; platelet transfusions can be given on an outpatient basis.

Usual length of stay for patients undergoing HDC in conjunction with TBI is about 30 days. Discharge parameters are similar to above: fever-free for 48 hours, adequate blood counts (WBC greater than 1,000). Patients may be discharged even if the continue to require platelet transfusions, as these transfusions can be given on an outpatient basis.

Studies on Autologous Transplant:

Takvorian and colleagues (1987) studied 49 patients with either high-grade (n = 29), intermediate-grade (n = 14) or low-grade (n = 6) lymphoma. All patients were considered to have a poor prognosis either due to relapse (n = 41) or poor prognostic factors (n = 8). These latter 8 patients were in at least partial remission but were considered to be at high-risk for relapse due to a bulky tumor mass, or multiple sites of extra-nodal involvement. All patients had a good performance status. The common feature of all these patients was that they were responsive to conventional induction therapy such that at the time of HDC, all patients had a minimal disease burden. In fact, 23 patients were considered to be in complete remission. A total of 34 of the 49 patients remained in complete remission for 2 to 52 months post-HDC, which translated into a 65% probability that patients would remain disease free for greater than 11 months. Two patients died from treatment-related toxicity and relapse occurred in 13 others. All relapses occurred before 11 months. Other earlier studies of HDC had included all patients relapsing from disease, regardless of their performance status or whether the lymphoma was chemo-resistant. In these studies the mortality rate ranged from 20 to 40% and long-term disease survival was seen in only 20% of patients. Considering their improved results, the authors suggested that HDC should be a treatment option for patients with relapsing disease but with a minimal tumor burden that is still responsive to chemotherapy.

Schouten et al (1994) reported their findings of 92 patients with low-grade NHL treated with HDC and ASCT. At the time of ASCT, the majority of patients had chemo-sensitive disease in first or subsequent remission (37%) or disease with a good response to chemotherapy (49%). At a median follow-up of 19 months, the progression free survival is 52%. Patients with complete remission or responding relapse at the time of ASCT had a significantly better progression-free survival compared to patients with refractory disease. Patients with transformed low-grade NHL at ASCT had a very poor outcome. Despite the relatively short follow-up of this study, the data suggested that chemo-sensitive disease responded better to HDC followed by stem cell transplant than refractory disease at the time of ASCT.

Mills and colleagues (1995) reported the main prognostic factors in 107 patients with relapsed or resistant intermediate- or high-grade NHL who underwent HDC with ASCT. All patients had failed to achieve a complete remission to conventional chemotherapy or had subsequently relapsed. Additionally, there was no bone marrow involvement in any of the patients. Forty-two patients (40%) had chemoresistant disease at the time of HDC, 55 (51%) had chemo-sensitive disease, and 10 (9%) had untreated relapse. At 3 months, 44 patients (41%) were assessed to be in complete remission, 34 (32%) were in partial remission and 22 (21%) showed no response or had progressive disease. There were 7 early procedure-related deaths. Overall survival rate at 5 years is 41% and progression free survival rate is 35%. None of the patients who were unresponsive to HDC survived beyond 18 months,
whereas at a median follow-up of 34 months, 50 % of the partial responders were alive. Patients with chemo-sensitive disease, small masses, and ASCT after one line of chemotherapy had the best outcome.

In a randomized clinical trial (The European CUP trial), Schouten et al (2003) examined if high-dose therapy (HDT) followed by ASCT is more effective than standard treatment with regard to progression-free survival (PFS) and overall survival (OS) in patients with relapsed follicular NHL; and evaluated the additional value of B-cell purging of the stem-cell graft with regards to PFS and OS. Patients received three cycles of chemotherapy. Responding patients with limited bone marrow infiltration were eligible for random assignment to 3 further cycles of chemotherapy (C), unpurged HDT (U), or purged HDT (P). A total of 140 patients were registered from 36 centers internationally, and 89 were randomly assigned. Reasons for not randomizing included patient refusal, early progression, or death on induction therapy. With a 69-month median follow-up, the log-rank P value for PFS and OS were 0.0037 and 0.079, respectively. The authors concluded that HDT significantly improves PFS and OS in patients under age of 60 years with recurrent chemosensitive disease. Furthermore, there is no clear evidence of benefit through purging. This is in agreement with the observations of Alvarnas and Forman (2004) who stated that data to justify routine use of hematopoietic stem cell graft purging are insufficient.

In a recent review on stem cell transplantation in follicular lymphoma, Tse et al (2004) stated that ASCT or allogeneic stem cell transplantation in first remission remains an investigational procedure.

A review (Sweetenham, 2001) states that the role of stem cell transplantation (autologous/allogeneic) in patients with mantle cell lymphoma is unclear. In particular, there is no justification for autologous stem cell transplantation in patients who have failed multiple lines of therapy, and its role in first remission is unproven. Furthermore, the role of allogeneic stem cell transplantation in mantle cell lymphoma is also unclear and unproven. Thus, the study concludes that stem cell transplantation for the treatment of mantle cell lymphoma should only be used as part of a clinical trial.

High-dose chemotherapy with ASCT has been proven effective in relapsed aggressive NHL. However, conflicting results of HDT as part of first-line treatment have been reported in randomized controlled trials (RCTs). In a Cochrane review, Greb et al (2008) examined if HDC with ASCT as part of first-line treatment improves survival in patients with aggressive NHL. Randomized controlled trials comparing conventional chemotherapy versus HDC in the first-line treatment of adults with aggressive NHL were included in this review. Eligibility and quality assessment, data extraction and analysis were done in duplicate. All authors were contacted to obtain missing data and asked to provide individual patient data. A total of 15 RCTs (n = 3079) were eligible for this meta-analysis. Overall treatment-related mortality was 6.0 % in the HDT group and not significantly different compared to conventional chemotherapy (odds ratio [OR] 1.33; 95 % confidence interval [CI]: 0.91 to 1.93, p = 0.14). A total of 13 studies (n = 2,018) showed significantly higher complete remission (CR) rates in the group receiving HDT (OR 1.32; 95 % CI: 1.09 to 1.59, p = 0.004). However, HDT did not have an effect on OS, when compared to conventional chemotherapy. The pooled hazard ratio (HR) was 1.04 (95 % CI: 0.91 to 1.18, p = 0.58). There was no statistical heterogeneity among the trials. Sensitivity analyses underlined the robustness of these results. Subgroup analysis of prognostic groups according to IPI did not show any survival difference between HDT and controls in 12 trials (low and low-intermediate risk IPI: HR 1.41; 95 % CI: 0.95 to 2.10, p = 0.09; high-intermediate and high risk IPI: HR 0.97; 95 % CI: 0.83 to 1.13, p = 0.71. Event-free survival (EFS) also showed no significant difference between HDT and CT (HR 0.93; 95 % CI: 0.81 to 1.07, p = 0.31). Other possible risk factors such as the proportion of patient with diffuse large cell lymphoma, protocol adherence, HDT strategy, response status before HDT, conditioning regimens and methodological issues were analyzed in sensitivity analyzes. However, there was no evidence for an association between these factors and the results of these analyses. The authors concluded that despite higher CR rates, there is no benefit for HDC with ASCT as a first-line treatment in patients with aggressive NHL.

In a phase-II clinical trial, Krishnan et al (2008) assessed the safety and effectiveness of combining yttrium-90 (90Y) ibritumomab tiuxetan (Zevalin) with high-dose carmustine, cytarabine, etoposide, and
melphalan (BEAM) and ASCT in patients with NHL who were ineligible for TBI because of older age or prior radiotherapy. A total of 41 patients with received standard-dose 90Y ibritumomab tiuxetan (14.8 MBq/kg [0.4 mCi/kg]) followed by high-dose BEAM. The median age was 60 years (range of 19 to 78 years), and the median number of previous therapies was 2 (range of 1 to 6). Disease histologies were diffuse large B-cell (n = 20), mantle cell (n = 13), follicular (n = 4), and transformed lymphoma (n = 4). With a median follow-up of 18.4 months (range of 5.5 to 53.3 months), the estimated 2-year OS and PFS were 88.9 % (95 % CI: 75.3 % to 95.2 %) and 69.8 % (95 % CI: 56.4 % to 79.7 %), respectively. The median time to white blood cell engraftment was 11 days (range of 9 to 26 days) and time to platelet engraftment was 12 days (range of 3 to 107 days). Adverse events were similar to those seen historically with high-dose BEAM alone, and included grade 3 or 4 pulmonary toxicity in 10 patients. The authors concluded that adding 90Y ibritumomab tiuxetan to high-dose BEAM with ASCT is feasible and has a toxicity and tolerability profile similar to that observed with BEAM alone. They noted that rates of PFS seen in these patients are promising and warrant additional study.

Seshadri et al (2009) stated that ASCT for relapsed/refractory aggressive NHL results in long-term disease-free survival in 40 to 50 % of patients. The incidence of and risk factors for second cancer development in these patients have not been well studied. These investigators analyzed 372 patients with relapsed/refractory aggressive NHL who underwent ASCT from 1987 to 2006. Median age at ASCT was 50 years (range of 19 to 70). Most patients (74 %) received two chemotherapy regimens before transplant. High-dose chemotherapy consisted of etoposide and melphalan in 95 % of patients and 16 % received TBI. A total of 32 patients (9 %) developed a second cancer (19 hematologic, 13 solid tumors). The probability of second cancer at 3 and 10 years post-ASCT was 4.4 % and 12.9 %, respectively. When compared with the general population, the relative risk of acute myeloid leukemia and new solid tumor was 13.2 (p < 0.0001) and 2.3 (p = 0.0013). Salvage therapy using mini-BEAM was significantly associated with second cancer development (p = 0.004). The authors concluded that second cancers are a significant cause of late morbidity and mortality patients treated with ASCT with curative intent, and appear increased in patients exposed to mini-BEAM chemotherapy.

Freytes and Lazarus (2009) stated that although ASCT is the only potentially curative treatment for lymphoma that has relapsed after conventional chemotherapy, the prognosis of patients with disease recurrence after auto-HSCT is poor. Some highly selected patients can benefit from second transplants. One-third with late recurrence after initial auto-HSCT may attain a prolonged remission after second auto-HSCT. Non-myeloablative or reduced-intensity conditioning (RIC) allogeneic hematopoietic SCT (allo-HSCT) has been used successfully after auto-HSCT failures, especially in subjects who have an HLA-compatible donor, chemo-sensitive disease and good performance status. Patients with chemo-sensitive disease recurrence who have completed at least 1 year after their first auto-HSCT should be considered for a second auto-HSCT. Patients who have chemo-resistant disease are best served by participation in a well-designed clinical trial examining novel anti-tumor agents.

Al Khabori et al (2012) stated that the impact of HDC and ASCT versus conventional-dose chemotherapy in the initial management of adults with advanced follicular lymphoma (FL) on OS remains uncertain. These investigators performed a systematic review of the RCTs addressing this question. They searched MEDLINE, EMBASE, CENTRAL, American Society of Hematology, American Society of Clinical Oncology, BIOSIS, PAPERSFIRST, PROCEEDINGS, clinical trials registries, and bibliographies of relevant studies for RCTs comparing myeloablative chemotherapy with ASCT to any chemotherapy in adults with untreated advanced FL. They performed a meta-analysis using random effects models to estimate OS, EFS, and risks of adverse outcomes. Statistical heterogeneity was calculated by using the I(2) statistic. A total of 7 trials proved eligible, 4 of which provided data from 941 patients that could be included in a meta-analysis and 3 of which remain unpublished. In 2 of the trials, patients in both arms received rituximab during the induction treatment. Moderate quality evidence from the 3 trials that reported OS (n = 701 patients) suggests that ASCT did not result in improved OS (HR of death = 0.99, 95 % CI: 0.73 to 1.33). Low-quality evidence from the 4 trials of 941 patients suggested improvement in EFS in favor of ASCT (HR of death = 0.54, 95 % CI: 0.36 to 0.82) with substantial heterogeneity (I(2) = 80 %). Adverse outcomes of treatment-related mortality (TRM), myelodysplastic syndrome, acute myeloid leukemia, and solid tumors were not different between the 2 arms (RR of
treatment-related mortality = 1.04, 95% CI: 0.29 to 3.70; RR of myelodysplastic syndrome/acute myeloid leukemia = 2.19, 95% CI: 0.45 to 10.55; I(2) = 48 %; and RR of solid tumors = 1.30, 95% CI: 1.33 to 5.08. The absolute risk of death from treatment was 14 per 1,000 patients for those who received chemotherapy and 15 per 1,000 for those who received ASCT (range of 4 to 52). The authors concluded that available evidence suggested that HDC and ASCT as part of FL initial treatment does not improve OS. They stated that future trials of ASCT in the context of current chemoimmunotherapy approaches to FL are needed.

Studies on Allogeneic Transplant:

Chopra and associates (1992) used a case-controlled analysis of the European Bone Marrow Transplant Registry data to compare allogeneic with autologous transplant for patients with NHL. A total of 101 matched sets of patients were studied. Although the relapse rate was lower with allogeneic transplant (23% compared to 48% at 31 to 48 months), the overall PFS rate was similar between the 2 groups (49% for allogeneic versus 46% for autologous). As expected the toxic death rate was higher among allogeneic transplants (28% versus 14%). Among the subgroups of lymphoma, allogeneic transplant only showed a survival advantage among the 16 patients with lymphoblastic lymphoma, perhaps due to a graft versus host anti-leukemic effect.

Tan and Bartlett (2000) noted that combination chemotherapy remains the standard of care for the treatment of aggressive NHL. Major advances in the management of aggressive lymphomas include validation of the international prognostic index and clarification of the role of high-dose therapy with bone marrow or stem cell transplantation in patients with relapsed aggressive lymphomas. Many randomized pilot trials of HDC as initial therapy for aggressive lymphomas have shown conflicting results and await confirmatory studies.

Hale and Phillips (2000) mentioned that certain poor-prognosis patients with NHL and Hodgkin's disease, usually with recurrent and/or refractory disease, are rarely curable with standard chemoradiotherapy. Autologous hematopoietic stem cell transplantation has been demonstrated to result in improved long-term disease-free survival in some of these patients. Unfortunately, a number of patients are not suitable for autologous transplantation due to a damaged stem cell pool involvement or other disease processes of the marrow. These patients may benefit from allogeneic stem cell transplantation. In addition to the therapeutic effect of HDC with or without TBI, an immunologic (i.e., graft-versus-lymphoma) effect may be present in some patients undergoing allogeneic transplantation, resulting in a lower relapse rate than that obtained from autologous transplantation. However, allogeneic transplantation is often associated with a higher non-relapse mortality due primarily to graft-versus-host disease.

In a review, Mink and Armitage (2001) stated that ASCT has proven to be beneficial in selected patients with Hodgkin's disease and NHL. For patients with diffuse large-cell NHL, transplantation can be considered standard therapy for relapsed patients if they have chemotherapy-sensitive disease. The use of transplantation for high-risk patients in complete remission is promising, but definite recommendations cannot be made at this time. For follicular lymphomas, selected patients seem to benefit and studies are ongoing. Finally, the use of autologous stem cell transplantation can be useful in a select group of younger patients.

Allogeneic SCT is an effective therapy for lymphoma. Reduced-intensity conditioning (RIC) reduces non-relapse mortality associated with myeloablative conditioning but relapse rates are high when performed in active disease. Shimoni et al (2008) examined the safety and outcome of ibritumomab tiuxetan combined with RIC in patients with advanced lymphoma. The study included 12 patients, median age 54 years (37 to 62), with a median of 4 prior treatments (2 to 6) and active disease documented on PET-CT. Zevalin 0.4 mCi/kg was given on day-14 and fludarabine combined with busulfan (n = 6) or melphalan (n = 6) was started on day-6. Graft-versus-host disease (GVHD) prevention was tapered 3 months after SCT to augment the graft-versus-lymphoma effect. All patients engrafted, a median of 14 days after SCT; 83% achieved CR/partial remission (PR). With a median follow-up of 21 months (12 to 37), 2-year PFS was 33%. Only 3 patients relapsed; cumulative
incidence 25%. Non-relapse mortality was 42%, predominantly due to acute GVHD. Zevalin-RIC is feasible with consistent engraftment, acceptable organ toxicity, but high rates of acute GVHD. The low incidence of relapse suggested augmented anti-lymphoma effect. The authors stated that Zevalin-RIC merits further study. Better results may be achieved in patients earlier in disease course and with longer duration of immune-suppression.

Lazarus and colleagues (2010) compared outcomes of 916 DLBCL patients aged 18 years or older undergoing first autologous (n = 837) or myeloablative (MA) allogeneic hematopoietic cell transplant (HCT) (n = 79) between 1995 and 2003 reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). Median follow-up was 81 months for allogeneic HCT versus 60 months for autologous HCT. Allogeneic HCT recipients were more likely to have high-risk disease features including higher stage, more prior chemotherapy regimens, and resistant disease. Allogeneic HCT was associated with a higher 1 year TRM (relative risk [RR] 4.88; 95% CI: 3.21 to 7.40, p < 0.001), treatment failure (RR 2.06; 95% CI: 1.54 to 2.75, p < 0.001), and mortality (RR 2.75; 95% CI: 2.03 to 3.72, p < 0.001). Risk of disease progression was similar in the 2 groups (RR 1.12; 95% CI: 0.73 to 1.72, p = 0.59). In fact, for 1-year survivors, no significant differences were observed for TRM, progression, PFS or OS. Increased risks of TRM and mortality were associated with older age (greater than 50 years), lower performance score, chemo-resistance, and earlier year of transplant. The authors concluded that in a cohort of mainly high-risk DLBCL patients, upfront MA allogeneic HCT, although associated with increased early mortality, was associated with a similar risk of disease progression compared to lower risk patients receiving autologous HCT.

van Kampen et al (2011) analyzed the outcome, including non-relapse mortality (NRM), relapse rate (RR), PFS, and OS, of patients with diffuse large B-cell non-Hodgkin’s lymphoma (DLBCL) relapsed after an ASCT and treated with a an allogeneic stem-cell transplantation (allo-SCT). The European Group for Blood and Marrow Transplantation database was scanned for a first allo-SCT in relapsed DLBCL after a previous ASCT between 1997 and 2006. Other inclusion criteria were age at allo-SCT greater than or equal to 18 years and availability of an HLA-identical sibling or a matched unrelated donor. A total of 101 patients (57 males; median age of 46 years) were included. Median follow-up for survivors was 36 months. Myeloablative conditioning regimen was used in 37 patients and RIC was used in 64 patients. Three-year NRM was 28.2% (95% CI: 20% to 39%), relapse rate was 30.1% (95% CI: 22% to 41%), PFS was 41.7% (95% CI: 32% to 52%), and OS was 53.8% (95% CI: 44% to 64%). Non-relapse mortality was significantly increased in patients greater than or equal to 45 years (p = 0.01) and in those with an early relapse (less than 12 months) after ASCT (p = 0.01). Relapse rate was significantly higher in refractory patients (p = 0.03). A time interval to relapse after ASCT of less than 12 months was associated with lower PFS (p = 0.03). The use of RIC regimens was followed by a trend to a lower NRM (p = 0.1) and a trend to a higher relapse rate (p = 0.1), with no differences in PFS and OS. No differences were seen between HLA-identical siblings and matched unrelated donors. The authors concluded that allo-SCT in relapsed DLBCL after ASCT is a promising therapeutic modality. Patients with a long remission after ASCT and with sensitive disease at allo-SCT are the best candidates for this approach.

Maura and associates (2016) noted that follicular lymphoma (FL) is the 2nd most common histotype of NHL, and it is generally characterized by a heterogeneous clinical course. Despite recent therapeutic and diagnostic improvements, a significant fraction of FL patients still relapsed. In younger and/or fit FL relapsed patients, BMT has represented the main salvage therapy for many years. Thanks to the ability of HDC to overcome the lymphoma resistance and refractoriness, ASCT can achieve a high CR and favorable outcome regarding PFS and OS; allo-SCT combines the HDC effect together with the immune reaction of the donor immune system against lymphoma, the so-called “graft versus lymphoma” (GVL) effect. Considering the generally higher TRM, allo-SCT is mostly indicated for FL relapsed after ASCT.

Picleanu and colleagues (2017) stated that allo-SCT is a therapeutic option for relapsed, advanced, and otherwise incurable NHL suggested by the existence of a graft-versus-lymphoma effect. The main complications are GVHD and infections. These investigators performed a retrospective analysis of patients with NHL, who received an allo-SCT between January 1995 and December 2014. The
parameters that had an impact on OS were age less than or equal to 60 years old, chemo-sensitive disease pre- allo-SCT, and indolent NHL histology. The parameters that had an impact on PFS were age less than or equal to 60 years old and chemo-sensitive disease pre- allo-SCT. Only aggressive NHL histology and refractory disease pre- allo-SCT showed an increased risk of death in the multivariate model. The use of allo- SCT for young patients with multiple relapsed chemo-sensitive indolent NHL is a suitable option. The authors concluded that despite poor prognosis, young aggressive NHL patients can be considered for allo- SCT provided they have chemo-sensitive disease.

Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are neoplasms of hematopoietic origin characterized by the accumulation of lymphocytes with a mature, generally well-differentiated morphology. In CLL, these cells accumulate in the blood, marrow, lymph nodes, and spleen, while in SLL they are generally confined to the lymph nodes. CLL and SLL share many common features and are often referred to as blood and tissue counterparts of each other. Both tend to occur in older individuals and present as asymptomatic enlargement of the lymph nodes. Both tend to be indolent in nature but can undergo transformation to a more aggressive form of disease. Treatment regimens used for CLL are generally the same as those used for SLL and outcomes of treatment are comparable for the 2 diseases. Both low- and intermediate-risk CLL and SLL demonstrate relatively good prognoses with median survivals of 6 to 10 years, while the median survival of high risk CLL or SLL may be only 2 years. Although typically responsive to initial therapy, CLL and SLL are rarely cured by conventional therapy and nearly all patients ultimately die of their disease. This natural history has prompted the investigation of HDC as a possible curative regimen.

Compared to applications of HDC and transplant in other NHLs, there is less literature regarding either autologous or allogeneic transplant for CLL. In general, allogeneic transplant appears to be the preferred treatment due to the obvious potential of marrow contamination with malignant cells associated with autologous transplant, and due to the potential for a beneficial graft versus disease effect when using allogeneic transplant. However, the lack of compatible donors and the older age of most patients limit the applicability of allogeneic transplant. The European Bone Marrow Transplantation Group (EBMTG) reported the results of allogeneic transplant in 47 patients with B-cell CLL treated between 1984 and 1992 (Michallet et al, 1993). All patients received HLA identical marrow donations. A total of 56 % were in Rai stage III or IV at the time of transplant. A total of 33 (70 %) of patients achieved a complete remission post-transplant and the projected probability of leukemia-free 5 year survival was 40 %. (It is unknown whether the diagnosis of complete remission is based on histologic or more sensitive molecular criteria.) The most important predictor of survival was stage at time of transplant. Those transplanted in stage 0- to II had a leukemia-free survival of 60 % compared to only 20 % for those transplanted in stage IV. This study, presented in abstract form only, provided no details regarding patient selection criteria or prior treatment. In addition, treatment related mortality is not reported. In an earlier summary from the EBMTG, 6 of 17 patients succumbed to treatment related mortality, primarily to graft versus host disease (Michallet et al, 1991). In another 1991 review of allogeneic transplant for CLL, Bandini et al estimated that the treatment related mortality was as high as 50 %.

Rabinowe et al (1993) reported on 20 patients with poor prognosis B-cell CLL who underwent either autologous (12 patients) or allogeneic (8 patients) bone marrow transplantation. Poor prognosis was defined as International Workshop on CLL Rai stage II-IV. Some patients had additional poor prognostic features such as diffuse involvement of the bone marrow, abnormal bone marrow cytogenetics or a rapid tumor growth rate. Additionally patients had to be less than 60 years old and had to have a minimal disease state at the time of transplant. Minimal disease state was defined as lymph nodes measuring less than 2 cm, absence of organomegaly and less than 20 % involvement of the bone marrow. Nine patients had been treated with chemotherapy prior to evaluation for transplant. The induction regimens varied and included primarily cyclophosphamide based regimens or fludarabine. Only 3 patients were in complete remission prior to transplant. Of the 8 patients receiving allogeneic transplants, 6 achieved a complete remission and remained in complete remission at a
median follow-up of 11.7 months. Of the 12 patients undergoing autologous transplant, 10 achieved a complete remission and remained in complete remission during a median follow-up of 5 months. There was only 1 treatment related death in a patient undergoing autologous transplant. The authors concluded that the above results were encouraging but that long-term follow-up is necessary to determine whether the high complete response rate will translate into increased patient survival.

Khouri et al (1994) also reported on a case-series study of 22 patients with CLL who were treated either with autologous (11 patients) or allogeneic (11 patients) transplant. Patient selection criteria for autologous transplant included marrow lymphocytosis of less than 15% at the time of transplant. The patient selection criteria for allogeneic transplant are unclear, and it is unclear whether chemo-sensitive disease was a requirement for either transplant option. All patients had relapsed after fludarabine therapy and the median number of prior chemotherapy regimens was 3. These patient selection criteria seem broader than those of Rabinowe, described above. In Khouri's series there was not a requirement for a minimal disease state, simply less than 15% involvement of the bone marrow for those undergoing autologous transplant. In fact, 8 and 4 patients had Rai stage IV and stage III disease respectively. At the time of transplant, no patient was in complete remission. Of the 11 patients who underwent autologous transplant, 6 achieved CR, 4 had only small foci of nodular lymphocytosis in the bone marrow (termed a nodular CR or nCR), and 1 patient had a partial remission. Three patients subsequently developed Richter's syndrome and died, and 2 others died in CR of infectious complications, leaving 3 patients alive in CR, 2 patients alive with relapsed disease and 1 patient alive in partial remission at a median of 10 months post-transplant. The autologous marrows were purged using an immunomagnetic technique. Nevertheless 5 had residual disease after purging as detected by flow cytometry. Although these patients received marrows contaminated with malignant cells, all achieved either a CR or nCR after transplant.

Of the 11 patients undergoing allogeneic transplant, 8 had stage IV disease, and 1 had stage III disease. Seven were resistant to fludarabine. Nevertheless, 7 patients achieved a CR, and 2 had a nCR. (1 patient achieved a partial remission after an initial transplant but subsequently achieved a nCR after a second allogeneic transplant.) One patient achieved a partial response and 1 patient died of infectious complications. Follow-up ranged from 2 to 36 months. The authors were particularly encouraged with the results of allogeneic transplant in this group of patients with advanced disease who, by their estimation, had a projected survival of only a few weeks.

Khouri et al (1998) at MD Anderson Cancer Center reported the results of allogeneic transplant in 10 patients with chemo-refractory and recurrent low-grade lymphomas. Two of these patients had diffuse well-differentiated lymphoma, which is the node-based equivalent to CLL. A total of 8 of the 10 patients achieved a CR and none have relapsed at a median follow-up of 816 days. The authors hypothesize that a beneficial graft versus leukemia effect may be partially responsible for these surprising results. This hypothesis is supported by the gradual disappearance of lymph node and bone marrow involvement, reminiscent of the graft versus leukemia effect that has been documented post-allogeneic transplant in patients with chronic myelogenous leukemia (CML). This article challenges the general assumption that high dose marrow ablative therapy is only effective in those patients who have chemo-sensitive disease.

In a review of the literature, van Besien et al (2001) concluded that randomized studies are needed to establish whether autologous transplantation confers a survival benefit over standard chemotherapy approaches. Allogeneic transplantation has a considerable treatment-related mortality, but durable remissions sometimes occur in patients with advanced disease. Further refinements of transplant techniques and properly designed prospective studies are necessary to establish the role of stem cell transplantation in the overall management of CLL.

Rai et al (2001) reported on new and emerging therapies for CLL. Both matched sibling and autologous stem cells transplants are far from proven as effective and appropriate except in a setting of prospective and peer-reviewed research protocol. Only when properly controlled clinical trials have been conducted can this treatment be considered for general use.
Although there is less published literature regarding either HDC with autologous or allogeneic transplant for CLL, HDC is regarded as a useful salvage treatment for this otherwise incurable disease. Early estimates of treatment related mortality as high as 50%, have not been confirmed by more recent studies from the American literature. Rabinowe et al (1993) and Khouri et al (1994) reported a 5 and 14% mortality rate among 20 and 22 patients respectively. These mortality rates are similar to those reported for other applications of HDC.

As expected, in this early stage of evolution of HDC for CLL, most patients treated had advanced disease. Even in this population of patients CR rates have generally been above 60% and the rates were not different between allogeneic and autologous transplants. Despite this encouraging intermediate outcome, there is limited data on long-term outcomes to determine whether HDC is curative or at the very least provides a significant improvement in survival. Given the results in patients with advanced disease, not unexpectedly there has been interest in offering this therapy earlier in the course of disease when the tumor burden may be lower and there is less chance of chemo-resistant disease. However, early in the course of disease the risk of HDC may become unacceptable when a prolonged indolent course is anticipated or when the patient has achieved a CR with fludarabine therapy.

Reljic et al (2015) stated that high-dose therapy (HDT) followed by auto-HCT is offered to patients with chronic lymphocytic leukemia (CLL) both as front-line consolidation and in the relapsed setting. The role of HDT in the front-line consolidation setting in CLL is uncertain. These investigators performed a literature search of PubMed and Cochrane until November 14, 2014 and the last 2 years of abstracts from relevant conferences. End-points included benefits (OS; progression-free survival [PFS]; event-free survival [EFS]) and harms (adverse events, secondary malignancies, TRM). The search identified 495 references of which 4 studies met inclusion criteria. Altogether, 301 patients were randomized to the HDT/auto-HCT arm and 299 patients to the control arm. Offering front-line HDT/auto-HCT did not result in statistically significant improvement in OS (HR = 0.91; 95% CI: 0.62 to 1.33) or PFS (HR = 0.70; 95% CI: 0.32 to 1.52). There was a statistically significant advantage favoring HDT/auto-HCT for EFS (HR = 0.46; 95% CI: 0.26 to 0.83). Moreover, HDT/auto-HCT did not result in higher rate of secondary malignancy (risk ratio [RR] = 1.06; 95% CI: 0.55 to 2.05) or TRM (RR = 1.32; 95% CI: 0.43 to 4.06). The authors concluded that offering HDT/auto-HCT as front-line consolidation in patients with CLL did not improve OS. Moreover, they stated that at present this approach should not be offered outside the context of a clinical trial.

An UpToDate review on “Treatment of relapsed or refractory chronic lymphocytic leukemia” (Rai and Stilgenbauer, 2015) states that “Investigational therapies -- Many agents are under active investigation. These include novel agents (e.g., Bruton's tyrosine kinase inhibitors other than ibrutinib, PI3-kinase inhibitors other than idelalisib, BCL-2 antagonists [ABT-199], and flavopiridol), combinations of agents already used in CLL; agents approved for other diseases (e.g., lenalidomide, dasatinib); and new antibodies (e.g., anti-CD37 antibodies). The only known curative therapy for CLL is allogeneic hematopoietic cell transplantation. However, most patients are not candidates for this approach. Ongoing studies are investigating the use of chimeric antigen receptor T cells (CAR-T cells) directed at CD19. As an example, an intriguing report described three patients with relapsed or refractory CLL who received autologous T cells modified with a lentiviral vector expressing chimeric antigen receptor with specificity for CD19, coupled with CD137 and CD3-zeta signaling domains after a preparatory regimen. All three patients demonstrated a tumor response, which persisted in one for at least 10 months. Toxicity included severe tumor lysis syndrome. Subsequent reports suggest that the efficacy in a larger population may be lower. Further follow-up of these patients and larger trials are needed to determine the efficacy of this approach”.

Primary Cutaneous T-Cell Lymphoma

Schlaak et al (2012) stated that primary cutaneous T-cell lymphomas (CTCL) belong to the group of NHL and usually run an indolent course. However, some patients progress to advanced tumor or leukemic stages. Up to now, no curative treatment has been established for those cases. In the last
few years, several publications have reported durable responses in some patients following allogeneic stem cell transplantation (alloSCT). In a Cochrane review, these researchers compared the safety and effectiveness of conventional therapies with alloSCT in patients with advanced primary cutaneous T-cell lymphomas. The search strategy included the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1950 to May 2011), Internet-databases of ongoing trials (www.controlled-trials.com; www.clinicaltrials.gov), conference proceedings of the American Society of Clinical Oncology (ASCO, 2009 to present) and the American Society of Hematology (ASH, 2009 to present). These investigators also contacted members of the European Organization for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Task Force to check for ongoing study activities. They hand-searched citations from identified trials and relevant review articles. In addition, RCTs from the European Group for Blood and Marrow Transplantation (EBMT) and International Conference on Cutaneous T-cell Lymphoma, ASCO and ASH up to 2010 were hand-searched. Genetically RCT comparing alloSCT plus conditioning therapy regardless of agents with conventional therapy as treatment for advanced CTCL were eligible to be included. From eligible studies, data were extracted found 2,077 citations, but none was relevant genetically or non-genetically RCTs. All 41 studies that were thought to be potentially suitable were excluded after full text screening for being non-randomized, not including CTCL or being review articles. The authors planned to report evidence from genetically or non-genetically RCTs comparing conventional therapy and alloSCT. However, no randomized trials addressing this question were identified. They stated that prospective genetically RCTs need to be initiated to evaluate the precise role of alloSCT in advanced CTCL.

Bo and colleagues (2016) examined clinical characteristics, response, outcome, and prognosis of peripheral blood stem cell transplantation (PBSCT) for patients with peripheral T-cell lymphoma (PTCL). This study retrospectively analyzed the effectiveness of PBSCT in 38 patients with PTCL. Kaplan-Meier methods were used in survival analysis, and the Cox regression model was applied in multivariate analysis; 10 clinical parameters were analyzed. The 2-year OS was 46 %, and the 5-year OS was 34 % after a median follow-up of 40 months. Patients who received allogeneic PBSCT (allo-PBSCT) had a higher non-relapse mortality than autologous PBSCT (auto-PBSCT), but they could achieve a longer-term disease-free survival (DFS) in the former, which OS could achieve 40 %. Survival analysis with Kaplan-Meier method showed the pre-transplant disease status, B symptoms (systemic symptoms of fever, night sweats, and weight loss), serum lactate dehydrogenase (LDH) in early (greater than 275 U/L), Eastern Cooperative Oncology Group (ECOG) score (greater than 1), prognostic index for PTCL score (greater than 2) were all prognostic factors for post-transplant OS. Pre-transplant disease status was the only prognostic factor for allo-PBSCT. The authors concluded that the key was to reducing transplant-related mortality of allo-PBSCT by RIC. Factors such as level of early serum LDH, extra-nodal involvement, B symptoms, ECOG score, Ann Arbor stage, and pre-transplant disease status were all related to the prognosis of patients treated with PBSCT. They stated that allo-PBSCT may be suggested as the first line therapy for late-stage PTCL patients who could reach treatment remission before transplantation.

El-Asmar and co-workers (2016) noted that no prospective, randomized trials exist comparing HDT followed by auto-HCT against conventional therapy for management of PTCL either as upfront consolidation or in the relapsed/refractory setting. Available data supporting this approach were limited to single-arm prospective or retrospective studies only. These researchers performed a systematic review/meta-analysis of the published literature; their search identified 1,586 publications, but only 27 (n = 1,368) met inclusion criteria. In the front-line setting, pooled analysis of only prospective studies showed rates of PFS of 33 % (95 % CI: 14 % to 56 %), OS of 54 % (95 % CI: 32 % to 75 %), relapse/progression of 26 % (95 % CI: 20 % to 33 %), and TRM of 2 % (95 % CI: 0 % to 5 %); for retrospective studies, rates of PFS, OS, relapse/progression, TRM, and secondary malignancies were 55 % (95 % CI: 40 % to 69 %), 68 % (95 % CI: 56 % to 78 %), 36 % (95 % CI: 24 % to 48 %), 6 % (95 % CI: 2 % to 11 %), and 7 % (95 % CI: 2 % to 14 %), respectively. On the other hand, pooled analysis of retrospective studies evaluating HDT/auto-HCT in the relapsed/refractory setting showed pooled rates of PFS, OS, relapse/progression, and TRM of 36 % (95 % CI: 32 % to 40 %), 47 % (95 % CI: 43 % to 51
Kitahara and associates (2017) stated that cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP)/CHOP-like chemotherapy has been mostly applied to patients with untreated PTCL. Because the long-term outcome of patients with PTCL, especially those achieving CR, has not been fully elucidated, these investigators retrospectively analyzed 78 consecutive patients initially treated with CHOP/CHOP-like chemotherapy, without HDC followed by autologous stem cell transplantation (HDC/auto-SCT). Median OS and PFS in all 78 patients were 44 and 17 months, respectively, with a median follow-up of 62 months. In the 53 patients achieving CR, the median relapse-free survival (RFS) was 21 months, and 2-, 3-, and 5-year RFSs were 46, 45, and 36 %, respectively. The authors concluded that although these findings showed an unfavorable outcome for PTCL as a whole, those who achieved CR following CHOP/CHOP-like chemotherapy did not always have a poor outcome without the consolidation of HDC/auto-SCT; in particular, 45 % of the 65 years or younger patients were alive without disease at 5 years.

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<th>CPT Codes / HCPCS Codes / ICD-10 Codes</th>
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<td>S2150</td>
<td>Bone marrow or blood-derived stem-cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre-and post-transplant care in the global definition</td>
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**Other HCPCS codes related to the CPB:**

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**ICD-10 codes covered if selection criteria are met:**

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<td>C82.00 - C96.9</td>
<td>Malignant neoplasm of lymphoid, hematopoietic and related tissue [except Hodgkin's disease]</td>
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**The above policy is based on the following references:**


88. Freytes CO, Lazarus HM. Second hematopoietic SCT for lymphoma patients who relapse after autotransplantation: Another autograft or switch to allograft? Bone Marrow Transplant. 2009;44(9):559-569.


Amendment to
Aetna Clinical Policy Bulletin Number: 0494
Hematopoietic Cell Transplantation for Non-Hodgkin's Lymphoma

For the Pennsylvania Medical Assistance plan, if the transplant institution’s criteria are met, then the transplant will be covered.