Name of Policy:  
Hematopoietic Stem Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Policy #: 398  
Category: Surgery  
Latest Review Date: January 2014  
Policy Grade: B

Background/Definitions:  
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
Description of Procedure or Service:  
Hematopoietic Stem-Cell Transplantation

Hematopoietic stem-cell transplantation (HSCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone marrow-toxic doses of cytotoxic drugs, with or without whole-body radiation therapy. Stem cells from bone marrow may be obtained from the transplant recipient (autologous HSCT, auto-HSCT) or from a donor (allogeneic HSCT, allo-HSCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naive” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused stem cells and the recipient is not an issue in auto-HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allo-HSCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA A, B, and DR loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

Conventional Preparative Conditioning for Hematopoietic HSCT

The conventional (“classical”) practice of allogeneic HSCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total-body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that develops after engraftment of allogeneic stem cells within the patient’s bone marrow space. The slower GVM effect is considered the potentially curative component, but it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HSCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HSCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient prior to undergoing bone marrow ablation. As a consequence, autologous HSCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.
Reduced-Intensity Conditioning for Allogeneic HSCT
Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden but also to minimize as much as possible associated treatment-related morbidity and nonrelapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HSCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For the purposes of this Policy, the term “reduced-intensity conditioning” will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

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 blood, bone marrow, lymph nodes, and spleen, while in SLL they are generally confined to lymph nodes. The Revised European-American/WHO Classification of Lymphoid Neoplasms considers B-cell CLL and SLL a single disease entity.

CLL and SLL share many common features and are often referred to as blood and tissue counterparts of each other, respectively. 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 (e.g., Richter’s transformation). The median age at diagnosis of CLL is approximately 72 years, but it may present in younger individuals, often as poor-risk disease with significantly reduced life expectancy.

Treatment regimens used for CLL are generally the same as those used for SLL, and outcomes of treatment are comparable for the two diseases. Both low- and intermediate-risk CLL and SLL demonstrate relatively good prognoses with median survivals of six to ten years, while the median survival of high-risk CLL or SLL may be only two 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 prompted investigation of hematopoietic stem-cell transplantation as a possible curative regimen.

Staging and Prognosis of CLL/SLL
Two scoring systems are used to determine stage and prognosis of patients with CLL/SLL. As outlined in Table 1, the Rai and Binet staging systems classify patients into three risk groups with different prognoses and are used to make therapeutic decisions.
Table 1. Rai and Binet Classification for CLL/SLL Rai Stage

<table>
<thead>
<tr>
<th>Rai Stage</th>
<th>Risk</th>
<th>Description</th>
<th>Median Survival (yr)</th>
<th>Binet Stage</th>
<th>Description</th>
<th>Median Survival (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>Lymphocytosis</td>
<td>&gt;10</td>
<td>A</td>
<td>3 or fewer lymphoid areas, normal hemoglobin and platelets</td>
<td>&gt;10</td>
</tr>
<tr>
<td>I</td>
<td>Intermediate</td>
<td>Lymphocytosis plus lymphadenopathy</td>
<td>7-9</td>
<td>B</td>
<td>3 or more lymphoid areas, normal hemoglobin and platelets</td>
<td>7</td>
</tr>
<tr>
<td>II</td>
<td>Intermediate</td>
<td>Lymphocytosis plus splenomegaly plus/minus lymphadenopathy</td>
<td>7-9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>High</td>
<td>Lymphocytosis plus anemia plus/minus lymphadenopathy or splenomegaly</td>
<td>1.5-5</td>
<td>C</td>
<td>Any number of lymphoid areas, anemia, thrombocytopenia</td>
<td>5</td>
</tr>
<tr>
<td>IV</td>
<td>High</td>
<td>Lymphocytosis plus thrombocytopenia plus/minus anemia, splenomegaly or lymphadenopathy</td>
<td>1.5-5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

lymphocytosis=lymphocytes >15 x 10^9/L for 4 wks; anemia=hemoglobin <110 g/L; thrombocytopenia=platelets <100 x 10^9/L

Because prognosis of patients varies within the different Rai and Binet classifications, other prognostic markers are used in conjunction with staging to determine clinical management. These are summarized in Table 2, according to availability in clinical centers.

Table 2. Markers of Poor Prognosis in CLL/SLL Community Center

<table>
<thead>
<tr>
<th>Community Center</th>
<th>Specialized Center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced Rai or Binet stage</td>
<td>IgVh wild type</td>
</tr>
<tr>
<td>Male sex</td>
<td>Expression of ZAP-70 protein</td>
</tr>
<tr>
<td>Atypical morphology or CLL/PLL</td>
<td>del 11q22-q23 (loss of ATM gene)</td>
</tr>
<tr>
<td>Peripheral lymphocyte doubling time &lt;12 months</td>
<td>del 17p13 (loss of p53)</td>
</tr>
<tr>
<td>CD38+</td>
<td>trisomy 12</td>
</tr>
<tr>
<td>Elevated beta2-microglobulin level</td>
<td>Elevated serum CD23</td>
</tr>
<tr>
<td>Diffuse marrow histology</td>
<td>Elevated serum tumor necrosis factor-a</td>
</tr>
<tr>
<td>Elevated serum lactate dehydrogenase</td>
<td>Elevated serum thymidine kinase</td>
</tr>
<tr>
<td>level</td>
<td></td>
</tr>
<tr>
<td>Fludarabine resistance</td>
<td></td>
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</tbody>
</table>
Reduced-Intensity Conditioning for Allogeneic HSCT
Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for RIC allogeneic HSCT. These include those patients whose age (typically older than 60 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen. A patient who relapses following a conventional myeloablative allogeneic HSCT could undergo a second myeloablative procedure if a suitable donor is available and his or her medical status would permit it. However, this type of patient would likely undergo RIC prior to a second allogeneic HSCT if a complete remission could be re-induced with chemotherapy.

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

Policy:
Effective for dates of service on or after February 1, 2012:
Autologous hematopoietic stem-cell transplantation does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational to treat chronic lymphocytic leukemia or small lymphocytic lymphoma.

Allogenic hematopoietic stem-cell transplantation meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage to treat chronic lymphocytic leukemia or small cell lymphocytic leukemia in patients with markers of poor-risk disease.

Effective for dates of service prior to February 1, 2012:
Autologous or allogeneic hematopoietic stem-cell transplantation does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational to treat chronic lymphocytic leukemia or small lymphocytic lymphoma.

*Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*
**Key Points:**
Both Technology Evaluation Center (TEC) Assessments indicated that in the absence of randomized trials, existing data were insufficient to permit scientific conclusions regarding the use of either procedure, limited by inter-study heterogeneity in patient’s baseline characteristics, procedural differences, sample size, and short follow-up. A direct comparative analysis from the International Bone Marrow Transplant Registry (IBMTR) commissioned by TEC in 2002 to analyze allo-HSCT results was insufficient to permit scientific conclusions on the net health outcome of this procedure for relapsed or refractory CLL or SLL.

Recent reviews discuss uncertainties with respect to the type of transplant (autologous vs. allogeneic), the intensity of pretransplant conditioning, the optimal timing of transplantation in the disease course, the baseline patient characteristics that best predict likelihood of clinical benefit from transplant, and the long-term risks of adverse outcomes. The conclusions reached in these reviews suggest that while auto-HSCT may prolong survival in selected patients with CLL or SLL, for example, those with chemotherapy-sensitive malignancy who had a good response to front-line therapy and transplanted early in the course of disease, it has not yet been shown to be curative.

**Autologous HSCT**
A systematic review of auto-HSCT for CLL or SLL that included nine prospective studies, none of which was randomized, further highlighted the difficulties of inter-study comparisons of this evidence on this treatment. The authors of the review concluded that in the absence of randomized, controlled studies, it is uncertain whether auto-HSCT is superior to conventional chemotherapy (or current chemo-immunotherapy) combinations as first-line consolidation treatment in CLL or SLL patients, regardless of disease risk, or as salvage therapy in those with relapsed disease. While auto-HSCT may achieve significant clinical response rates (74%–100%) with relatively low treatment-related mortality (0–9%), molecular remissions are typically short lived, with subsequent relapse. Secondary myelodysplasia and myelodysplastic syndrome that may progress to frank acute myelogenous leukemia has been reported in 5%–12% of patients in some studies of auto-HSCT, which suggests caution in considering this approach, especially given the indolent nature of CLL or SLL.

The conclusions of the systematic review of autologous HSCT outlined above are congruent with results of a Phase III randomized trial published in 2010 that compared autologous HSCT (n=112) or post-induction observation (n=111) for consolidation in patients with CLL who were in complete remission (CR; 59% of total) or very good partial remission (PR; 27% of total) following fludarabine-containing induction therapy. Patient age ranged from 31-65 years, with Binet stage A progressive (14%), B (66%), and C (20%) disease. None were known to have 17p deletion; 45% were known to not carry 17p deletion, but that status was unknown in 54% of all patients. The primary outcome, median event-free survival (EFS), was 51 months (range: 40-62 months) in the autograft group, compared to 24 months (range: 17-32 months) in the observed group; the five-year EFS was 42% and 24%, respectively (p<0.001). The relapse rate at five-year follow-up was 54% in the autograft group versus 76% in the observational group (p<0.001); median time to relapse requiring therapy or to death (whichever came first) was 65 months.
(range: 59-71 months) and 40 months (range: 25-56 months), respectively (p=0.002). Overall survival probability at five-year follow-up was 86% (95% confidence interval [CI]: 77-94%) in the autograft arm, versus 84% (95% CI: 75-93%) in the observation arm (p=0.77), with no evidence of a plateau in the curves. There was no significant difference in NRM between groups, 4% in the autologous HSCT group and 0% in the observation group (p=0.33). Myelodysplastic syndrome (MDS) was observed at follow-up in three patients receiving an autograft and in one patient in the observational group.

In a subsequent report published in 2013, the authors of the European Intergroup RCT presented quality of life (QoL) findings from this trial. Two secondary analyses were performed to further investigate the impact of HSCT and relapse on QoL. In the primary analysis, the authors demonstrate an adverse impact of HSCT on QoL which was largest at four months and continued throughout the first year after randomization. Further, a sustained adverse impact of relapse on QoL was observed which worsened over time. Thus, despite better disease control by autologous HSCT the side effects turned the net effect towards inferior QoL in the first year and comparable QoL in the following two years after randomization.

Another prospective, randomized clinical trial assessed the efficacy of autologous HSCT in previously untreated CLL patients. A total of 244 patients (181 males) of median age 56 years (range 31-66 years) had Binet stage B (n=185) or C (n=56) disease. Among enrollees, 237 started planned therapy, six of whom discontinued. All 231 patients underwent induction chemotherapy; 103 (45%) entered CR and were randomly allocated to autologous HSCT (n=52) or observation (n=53). The three-year estimated OS rates were 98% (95% CI: 94%, 100%) in the observation arm, and 96% (95% CI: 90%, 100%) in the HSCT arm (p=0.73). The estimated HR for death was 1.2 (95% CI: 0.3, 3.8) in the HSCT arm relative to the observation arm (p=0.82). During the 36 months after randomization, HSCT was associated, on average, with an extra nine months without clinical symptoms or blood signs of CLL progression (32 ± 1 month) compared with observation (23 ± 2 months).

The results of the GOELAMS LLC 98 randomized trial became available online in July 2011, but were published in final form in 2012. This trial was aimed to compare two strategies in previously untreated high-risk CLL patients 60 years-old or younger. Arm A comprised conventional chemotherapy of six monthly courses of CHOP (vincristine, doxorubicin, and oral prednisone) followed by six additional CHOP courses every three months in patients who achieved a partial response (PR) or complete response (CR). Arm B consisted of three monthly CHOP courses; patients who achieved a very good partial response (VGPR) or CR received consolidation therapy consisting of high-dose cyclophosphamide plus total-body irradiation followed by autologous HSCT; rituximab was not used in this study. Among 86 total patients, 39 and 43 were evaluable in Arm A and B, respectively. The primary outcome was progression-free survival (PFS); on an intent-to-treat basis, the median PFS reached 22 months in Arm A and 53 months in Arm B at median follow-up of 77 months (p<0.0001). Median OS time, however, was 104.7 months (95% CI: 99.9, 109.5 months) in Arm A and 107.4 months (95% CI: 58.2, 156.6 months) in Arm B, a non-significant difference. This trial shows that front-line high-dose therapy with autologous HSCT prolongs PFS but does not significantly improve the duration of OS.
Allogeneic HSCT
Given that autologous HSCT based on myeloablative conditioning regimens has not been demonstrated to be a curative treatment of CLL/SLL, alternative modalities have been sought. Allogeneic HSCT has been under investigation for the past two decades based on a potent graft-versus-leukemia (GVL) effect expressed as a permanently active cellular immune therapy in the recipient, independent of chemotherapy-related cytotoxicity. As indicated in the Description section of this policy, allogeneic HSCT may include use of myeloablative or reduced-intensity pretransplant conditioning regimens.

Data compiled in numerous review articles suggest that myeloablative allogeneic HSCT has curative potential for CLL or SLL. Long-term disease control (33-65% OS at three to six years) due to a low rate of late recurrences has been observed in all published series, regardless of donor source or conditioning regimen. However, high rates (24-47%) of treatment-related mortality (TRM) discourage this approach in early or lower-risk disease, particularly among older patients whose health status typically precludes the use of myeloablative conditioning.

The development of reduced-intensity conditioning (RIC) regimens has extended the use of allogeneic HSCT to older or less fit patients who account for the larger proportion of this disease than younger patients, as outlined in several recent review articles. Six published nonrandomized studies involved a total of 328 patients with advanced CLL who underwent RIC allogeneic HSCT using conditioning regimens that included fludarabine in various combinations that included cyclophosphamide, busulfan, rituximab, alemtuzumab, and total-body irradiation. The majority of patients in these series were heavily pretreated, with a median three to five courses of prior regimens. Among individual studies, 27-57% of patients had chemotherapy-refractory disease, genetic abnormalities including del 17p13, del 11q22, and VH unmutated, or a combination of those characteristics. A substantial proportion in each study (18-67%) received stem cells from a donor other than an HLA-identical sibling. Reported NRM, associated primarily with graft-versus-host disease (GVHD) and its complications, ranged from 2% at 100 days to 26% overall at median follow-up that ranged from 1.7 years to five years. Overall survival rates ranged from 48-70% at follow-up that ranged from two to five years. Similar results were reported for progression-free survival (PFS), 34-58% at two to five year follow-up. Very similar results were reported from a Phase II study published in 2010 of RIC allogeneic HSCT in patients (n=90; median age 53 years, range: 27-65 years) with poor-risk CLL, defined as having one of the following: refractoriness or early relapse (i.e., less than 12 months) after purine-analog therapy; relapse after autologous HSCT; or, progressive disease in the presence of an unfavorable genetic marker (11q or 17p deletion, and/or unmutilated IgVh status and/or usage of the VH3-21 gene). With a median follow-up of 46 months, four-year NRM, EFS, and OS were 23%, 42%, and 65%, respectively. EFS was similar for all genetic subsets, including those with a 17p deletion mutation.

Summary
A substantial body of evidence from single-arm prospective and registry-based studies suggests allogeneic HSCT can provide long-term disease control and overall survival in patients with poor-risk CLL/SLL and otherwise dismal prognosis. This conclusion is supported by clinical input from transplant specialists as noted below. Until recently, it has been unclear what patient- and disease-specific characteristics can be used to select patients who could benefit from
allogeneic HSCT compared to those for whom less-intense or no therapy may be indicated. This question has been addressed by investigations of cytogenetic and molecular abnormalities that can be associated with differential response to various therapies. Some of these are outlined in Table 2 previously.

Autologous HSCT is feasible in younger patients but is not curative, particularly in those with poor-risk CLL. None of the studies of autologous HSCT published to date has shown a plateau in overall survival (OS) at four to six years post-transplant. It may result in prolongation of overall survival, compared with conventional therapy, but this must be considered in the context of improved outcomes using conventional chemoimmunotherapy. Furthermore, evidence from the European Intergroup RCT suggests QoL issues are important in selecting patients for autologous HSCT and may dictate the management course for individuals who are otherwise candidates for this approach.

Practice Guidelines and Position Statements

European Group for Blood and Marrow Transplantation (EBMT)
In June 2005, the EBMT convened a consensus panel to identify situations in which allogeneic HSCT is indicated for patients with CLL. Information for this evidence-based consensus was based on a MEDLINE search, meeting abstracts, and unpublished investigator-derived data. The panel considered four key issues:

- Does graft-versus-leukemia (GVL) activity in CLL exist?
- If yes, is it effective in high-risk CLL?
- What is the success rate of allogeneic HSCT in CLL?
- Which prognostic risk level justifies allogeneic HSCT?

The EBMT panel concluded that sound evidence exists that GVL activity is effective and represents the main contributor to durable disease control after allogeneic HSCT, even in poor-risk patients. It further concluded that long-term disease-free survival and possibly cure may be achieved in 33-67% of patients who undergo allogeneic HSCT for poor-risk CLL. Although allogeneic HSCT for CLL is a procedure with evidence-based efficacy for poor-risk CLL, evidence is not sufficient to identify a generally superior conditioning regimen. The optimum choice of conditioning regimens may vary: in the presence of older age, comorbidity and sensitive disease; RIC regimens might be appropriate, whereas myeloablative regimens might be preferable in younger patients with good performance status but poorly controlled disease. The EBMT statement further suggests that these cases be discussed with a transplant center as early as possible to avoid extensive cytotoxic pretreatment or disease transformation. Furthermore, because the optimum transplant strategy may vary according to the clinical situation, it should be defined whenever possible in approved prospective clinical protocols.

National Cancer Institute (NCI) Working Group on CLL
In 1988 and 1996, a National Cancer Institute Working Group (NCI-WG) on CLL published guidelines for the design and conduct of clinical trials to facilitate comparisons between treatments and establish definitions that could be used in scientific studies on the biology of this disease. The U.S. Food and Drug Administration (FDA) also adopted these guidelines in their evaluation and approval of new agents. An updated version of the NCI-WG guidelines has been
published that provides management recommendations based on new prognostic markers, diagnostic parameters, and treatment options.

**National Comprehensive Cancer Network (NCCN) Guidelines**

Current NCCN Guidelines (v1.2014) for non-Hodgkin’s lymphoma do not include autologous HSCT as a therapeutic option in CLL or SLL. NCCN indicates that allogeneic HSCT (conditioning regimen unspecified) may be considered, preferably in a clinical trial, for patients younger than age 70 years with high-risk disease (Rai high risk, or del17p,11q) or as salvage treatment in those with progressive or relapsed disease.

**Key Words:**
Chronic Lymphocytic Leukemia, High-Dose Chemotherapy

**Approved by Governing Bodies:**
Not applicable

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

**Current Coding:**
CPT Codes:

- **38204** Management of recipient hematopoietic 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
- **38208** Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing; per donor
- **38209** ;thawing of previously frozen harvest, with washing; per donor
- **38210** ;specific cell depletion with harvest, T-cell depletion
- **38211** ;tumor cell depletion
- **38212** ;red blood cell removal
- **38213** ;platelet depletion
- **38214** ;plasma (volume) depletion
- **38215** ;cell concentration in plasma, mononuclear, or buffy coat layer
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38220</td>
<td>Bone marrow, aspiration only</td>
</tr>
<tr>
<td>38221</td>
<td>;biopsy, needle or trocar</td>
</tr>
<tr>
<td>38240</td>
<td>Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic</td>
</tr>
<tr>
<td>38241</td>
<td>Bone marrow or blood-derived peripheral stem-cell transplantation; autologous</td>
</tr>
<tr>
<td>38242</td>
<td>;allogeneic donor lymphocyte infusions</td>
</tr>
</tbody>
</table>

**HCPCS:**

- **S2140** Cord blood harvesting for transplantation, allogeneic
- **S2142** Cord blood-derived stem cell transplantation, allogeneic
- **S2150** Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical, surgical, diagnostic, and emergency services)

**References:**


Policy History:

Medical Policy Group, February 2010 (3)
Medical Policy Administration Committee, February 2010
Available for comment February 23-April 8, 2010
Medical Policy Group, February 2012 (3): 2012 Updates- Description, Policy, Key Points, References
Medical Policy Administration Committee, February 2012
Available for comment February 22 through April 7, 2012
Medical Policy Panel, January 2013
Medical Policy Group, January 2013 (3): 2013 Updates: Key Points and References
Medical Policy Panel, January 2014
Medical Policy Group, January 2014 (3): Updates to Description, Key Points and References; no change in policy statement

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.