Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Policy Number: 8.01.15
Last Review: 6/2020
Origination: 12/2001
Next Review: 6/2021

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for hematopoietic cell transplantation for chronic lymphocytic leukemia and small lymphocytic lymphoma when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Allogeneic hematopoietic cell transplantation may be considered medically necessary to treat chronic lymphocytic leukemia or small cell lymphocytic lymphoma in patients with markers of poor-risk disease (see Considerations section). Use of a myeloablative or reduced-intensity pretransplant conditioning regimen should be individualized based on factors that include patient age, the presence of comorbidities, and disease burden.

When Policy Topic is not covered
Allogeneic hematopoietic cell transplantation is considered investigational to treat chronic lymphocytic leukemia or small lymphocytic lymphoma except as noted above.

Autologous hematopoietic cell transplantation is considered investigational to treat chronic lymphocytic leukemia or small lymphocytic lymphoma.

Considerations
Staging and Prognosis of CLL/SLL
Two scoring systems are used to determine stage and prognosis of patients with CLL/SLL. As outlined in the Table 1, the Rai and Binet staging systems classify patients into 3 risk groups with different prognoses, and are used to make therapeutic decisions.
### Table 1. Rai and Binet Classification for CLL/SLL

<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>


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.(1) These are summarized in Table 2, according to availability in clinical centers.

### Table 2. Markers of Poor Prognosis in CLL/SLL

<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 mos</td>
<td>• del 17p13/mutation TP53</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 level</td>
<td>• Elevated serum thymidine kinase</td>
</tr>
<tr>
<td>• Fludarabine resistance</td>
<td></td>
</tr>
</tbody>
</table>

CLL: chronic lymphocytic leukemia; SLL: small lymphocytic leukemia.

An expert panel convened by the American Society for Blood and Marrow Transplantation was queried about criteria used to define high-risk CLL, as part of the process for developing 2016 guidelines. Panelists responded that criteria are presence of del17P and/or TP53 mutations (100%) and presence of complex karyotype (67%).
Reduced-Intensity Conditioning for Allogeneic Hematopoietic Cell Transplantation

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for RIC allogeneic HCT. 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 HCT 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 (6 of 6). 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, haploidentical donors - typically a parent or a child of the patient - with whom usually there is sharing of only 3 of the 6 major histocompatibility antigens, have been under investigation as a stem-cell source. 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.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals: With chronic lymphocytic leukemia/small lymphocytic lymphoma and markers of poor-risk disease</td>
<td>Interventions of interest are: - Allogeneic hematopoietic cell transplantation</td>
<td>Comparators of interest are: - Chemotherapy and/or immunotherapy</td>
<td>Relevant outcomes include: - Overall survival - Disease-specific survival - Change in disease status - Treatment-related mortality - Treatment-related morbidity</td>
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</tr>
</tbody>
</table>

Risk stratification of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) guides therapy decisions, which may include hematopoietic cell transplantation for those with poor risk features.

For individuals who have CLL/SLL and markers of poor-risk disease who receive allogeneic hematopoietic cell transplantation (allo-HCT), the evidence includes
single-arm prospective and registry-based studies as well as a TEC Assessment. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related mortality and morbidity. Data have suggested that allo-HCT can provide long-term disease control and overall survival in patients with poor-risk CLL/SLL. High rates of treatment-related morbidity discourage this approach in lower risk disease, particularly among older patients whose health status typically precludes the use of myeloablative conditioning. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have CLL/SLL who receive autologous HCT, the evidence includes randomized controlled trials (RCTs), systematic reviews, and a TEC Assessment. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related mortality and morbidity. Autologous HCT is feasible in younger patients but is not curative, particularly in those with poor-risk CLL. Studies of autologous HCT published to date have not shown improvement in overall survival in patients with CLL/SLL, and results must be considered in the context of improved outcomes with the use of newer chemoimmunotherapy agents. Furthermore, evidence from the European Intergroup RCT has suggested quality-of-life issues are important in selecting patients for autologous HCT and may dictate the management course for patients who are otherwise candidates for this approach. The evidence is insufficient to determine the effects of the technology on health outcomes.

Background

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; in SLL they are generally confined to lymph nodes. The Revised European-American/World Health Organization 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 present as asymptomatic enlargement of the lymph nodes, tend to be indolent in nature, but can undergo transformation to a more aggressive form of disease (eg, Richter 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 treatment outcomes are comparable for both diseases. Both low- and intermediate-risk CLL and SLL demonstrate relatively good prognoses, with median survivals of 6 to 10 years; however, the median survival of high-risk CLL or SLL may only be 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 disease history prompted investigation of HCT as a possible curative regimen.

**Hematopoietic Cell Transplantation**

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

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is critical for achieving a good outcome of allo-HCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the 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.

**Conditioning for HCT**

**Conventional Conditioning for HCT**

The conventional practice of allo-HCT involves administration of cytotoxic agents (eg, 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 preengraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allo-HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to 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 before undergoing bone marrow ablation. As a consequence, autologous
HCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

**Reduced-Intensity Conditioning for Allo-HCT**

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 allo-HCT initially demonstrate donor cell engraftment and bone marrow–mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For this evidence review, the term *reduced-intensity conditioning* will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

**Regulatory Status**

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under the Code of Federal Regulation title 21, parts 1270 and 1271. Hematopoietic cells are included in these regulations.

**Rationale**

This evidence review was created in July 1999 and has been updated regularly with searches of the MEDLINE and EMBASE databases. The most recent literature update was performed through November 1, 2019.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more
intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

The original review was based on 2 TEC Assessments, 1 from 1999 that examined autologous hematopoietic cell transplantation (HCT) for chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL)\(^1\); the other from 2002 on allogeneic HCT (allo-HCT) to treat CLL and SLL.\(^2\) Both assessments indicated that existing data were insufficient to permit scientific conclusions on the use of either procedure, and were limited by interstudy heterogeneity in patients' baseline characteristics, procedural differences, sample size, and short follow-up. A direct comparative analysis from the International Bone Marrow Transplant Registry commissioned by TEC in 2002 to analyze allo-HCT results was insufficient to permit scientific conclusions on the net health outcome of this procedure for relapsed or refractory CLL or SLL.

Subsequent reviews through 2008 have discussed uncertainties concerning 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.\(^3,4,5,6,7,8\) The conclusions reached at that time suggested that, although autologous HCT may prolong survival in select patients with CLL or SLL (eg, those with chemotherapy-sensitive malignancy who had a good response to front-line therapy and were transplanted early in the course of disease), it had not yet been shown to be curative.

**ALLOGENEIC HCT**

**Clinical Context and Therapy Purpose**
The purpose of allogeneic HCT in patients who have CLL or SLL and markers of poor-risk disease is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: does allogeneic HCT improve the net health outcome in patients with CLL or SLL and markers of poor-risk disease.

The following PICOs were used to select literature to inform this review.
Patients
The relevant populations of interest are patients with CLL or SLL and markers of poor-risk disease.

Interventions
The therapy being considered is allogeneic HCT

Comparators
The following therapies are currently being used to treat CLL and SLL: chemotherapy and/or immunotherapy.

Outcomes
The general outcomes of interest are disease status, morbidity and mortality.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

Data compiled in review articles through 2012 suggested that myeloablative allo-HCT has curative potential for CLL or SLL. Long-term disease control (33%-65% overall survival [OS] at 3-6 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 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 regimens has extended the use of allo-HCT to older or less fit patients who account for the larger proportion of this disease than younger patients, as outlined in two 2009 review articles. Six published nonrandomized studies involved a total of 328 patients with advanced CLL who underwent reduced-intensity conditioning allo-HCT using regimens that included fludarabine in various combinations including cyclophosphamide, busulfan, rituximab, alemtuzumab, and total body irradiation. Most patients in these series were heavily pretreated, with a median of 3 to 5 courses of prior regimens. Among individual studies, 27% to 57% of patients had the chemotherapy-refractory disease, genetic abnormalities including a 17p13 deletion, 11q22 deletion, 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 a human leukocyte antigen identical sibling. Reported nonrelapse mortality associated primarily with graft-versus-host disease
and its complications ranged from 2% at 100 days to 26% overall at median follow-up ranging from 1.7 to 5 years. OS rates ranged from 48% to 70% at follow-up that ranged from 2 to 5 years. Similar results were reported for progression-free survival (PFS), which was 34% to 58% at 2- to 5-year follow-up. Very similar results were reported from a phase 2 study published in 2010 evaluating use of reduced-intensity conditioning allo-HCT in patients (n=90; median age, 53 years; range, 27-65) with poor-risk CLL, defined as having one of the following: refractoriness or early relapse (ie, <12 months) after purine-analogue therapy; relapse after autologous HCT; or progressive disease in the presence of an unfavorable genetic marker (11q or 17p deletion, and/or unmutated immunoglobulin heavy-chain variable-region status and/or usage of the VH3-21 gene).18 With a median follow-up of 46 months, 4-year NRM, event-free survival (EFS), and OS rates were 23%, 42%, and 65%, respectively. EFS estimates were similar for all genetic subsets, including those with a 17p deletion.

**Section Summary: Allogeneic HCT**
No RCTs evaluating allo-HCT in patients with CLL were identified. Data from nonrandomized studies found OS rates between 48% and 70% at 2 to 5 years and PFS rates of 34% to 58% at 2 to 5 years after allo-HCT for poor-risk CLL. Despite not being randomized, these studies suggest that allo-HCT can provide long-term disease control and OS in patients with poor-risk CLL and SLL.

**Autologous HCT**

**Clinical Context and Therapy Purpose**
The purpose of autologous HCT in patients who have CLL or SLL is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: does autologous HCT improve the net health outcome in patients with CLL or SLL?

The following PICOs were used to select literature to inform this review.

**Patients**
The relevant populations of interest are patients with CLL or SLL.

**Interventions**
The therapy being considered is autologous HCT.

**Comparators**
The following therapies are currently being used to treat CLL and SLL: chemotherapy and/or immunotherapy.

**Outcomes**
The general outcomes of interest are disease status, morbidity and mortality.

Study Selection Criteria Methodologically credible studies were selected using principles described above.
**Review of Evidence**

A 2015 systematic review of autologous HCT as the first-line consolidation in CLL included a literature search through November 2014. Four RCTs in adults were selected. Outcomes included OS, PFS, EFS, and harms (adverse events, treatment-related mortality, secondary malignancies). In these 4 trials, 301 patients were randomized to the autologous HCT arm and 299 to the control arm using first-line therapy without HCT as consolidation. Autologous HCT did not result in a statistically significant improvement in OS (hazard ratio, 0.91; 95% confidence interval [CI], 0.62 to 1.33) or in PFS (hazard ratio, 0.70; 95% CI, 0.32 to 1.52). There was a statistically significant improvement in EFS favoring autologous HCT (hazard ratio, 0.46; 95% CI, 0.26 to 0.83). A higher rate of secondary malignancy or treatment-related mortality was not associated with autologous HCT.

A phase 3 European Intergroup RCT (2011) evaluated autologous HCT as second- or third-line treatment of CLL. The trial compared autologous HCT (n=112) with postinduction observation (n=111) for consolidation in patients with CLL who achieved a complete response (59% of total) or very good partial response (27% of total) following fludarabine-containing induction therapy. Overall, patients' age ranged from 31 to 65 years, and they presented with Binet stage A progressive (14%), B (66%), and C (20%) disease. The population either did not have a 17p deletion or 17p deletion status was unknown. Median EFS (the primary outcome) was 51 months (range, 40-62 months) in the autograft group and 24 months (range, 17-32 months) in the observation group; 5-year EFS rates were 42% and 24%, respectively (p<0.001). The relapse rate at 5-year follow-up was 54% in the autograft group and 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). OS probability at 5-year follow-up was 86% (95% CI, 77% to 94%) in the autograft arm and 84% (95% CI, 75% to 93%) in the observation arm (p=0.77), with no evidence of a plateau in the areas under the curve. There was no significant difference in nonrelapse morality between groups (4% for autologous HCT vs 0% for observation; p=0.33). The myelodysplastic syndrome was observed at follow-up in 3 patients receiving an autograft and in 1 patient in the observational group.

In a subsequent 2014 report, authors of the European Intergroup RCT presented quality of life (QOL) findings from this trial. Two secondary analyses were performed to investigate the impact of HCT and relapse on QOL. In the primary analysis, the authors demonstrated an adverse impact of HCT on QOL, which was largest at 4 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 HCT, the side effects turned the net effect toward inferior QOL in the first year and comparable QOL in the following 2 years after randomization.
**Section Summary: Autologous HCT**
A systematic review of RCTs did not find that autologous HCT as first-line consolidation therapy for CLL significantly improved OS or PFS compared with alternative treatments. An RCT evaluating autologous HCT as second- or third-line treatment of CLL did not find that HCT improved the net health outcome.

**Summary of Evidence**
For individuals who have CLL/SLL and markers of poor-risk disease who receive allo-HCT, the evidence includes single-arm prospective and registry-based studies as well as a TEC Assessment. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related mortality and morbidity. Data have suggested that allo-HCT can provide long-term disease control and overall survival in patients with poor-risk CLL/SLL. High rates of treatment-related morbidity discourage this approach in lower risk disease, particularly among older patients whose health status typically precludes the use of myeloablative conditioning. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have CLL/SLL who receive autologous HCT, the evidence includes randomized controlled trials, systematic reviews, and a TEC Assessment. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related mortality and morbidity. Autologous HCT is feasible in younger patients but is not curative, particularly in those with poor-risk CLL. Studies of autologous HCT published to date have not shown improvement in overall survival in patients with CLL/SLL, and results must be considered in the context of improved outcomes with the use of newer chemoimmunotherapy agents. Furthermore, evidence from the European Intergroup randomized controlled trial has suggested the quality of life issues are important in selecting patients for autologous HCT and may dictate the management course for patients who are otherwise candidates for this approach. The evidence is insufficient to determine the effects of the technology on health outcomes.

**SUPPLEMENTAL INFORMATION**

**Clinical Input From Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 1 specialty medical center reviewer, 1 academic medical center reviewer, and 2 Blue Distinction Center reviewers while this policy was under review in 2010. Three of 4 reviewers agreed that allogeneic hematopoietic cell transplantation was of value to patients with poor-risk chronic lymphocytic leukemia (see Policy Guidelines section) and that
this procedure should be medically necessary for this setting. However, reviewers indicated that the specific approach (eg, reduced-intensity conditioning vs myeloablative conditioning) should be individualized based on criteria such as age and health status. All reviewers concurred with the policy statement that autologous HCT is investigational.

**Practice Guidelines and Position Statements**

**American Society for Blood and Marrow Transplantation**

In 2015, the American Society for Blood and Marrow Transplantation published guidelines on indications for allogeneic (allo-) and autologous hematopoietic cell transplantation (HCT) for chronic lymphocytic leukemia (CLL). Recommendations described the current consensus on the use of HCT in and out of the clinical trial setting. Treatment recommendations are shown in Table 1.

**Table 1. 2015 Recommendations for Allogeneic and Autologous HCT for CLL**

<table>
<thead>
<tr>
<th>Adult Indications</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk, first or greater remission</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>T cell, prolymphocytic leukemia</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>B cell, prolymphocytic leukemia</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Transformation to high-grade lymphoma</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>

C: standard of care, clinical evidence available; CLL: chronic lymphocytic leukemia; HCT: hematopoietic cell transplantation; N: not generally recommended; R: standard of care, rare indication.

In 2016, the Society published clinical practice recommendations with additional detail on allo-HCT for CLL. Recommendations are shown in Table 2.

**Table 2. 2016 Recommendations for Allogeneic HCT for CLL**

<table>
<thead>
<tr>
<th>Indications</th>
<th>Allogeneic HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk CLL</td>
<td>Not recommended in the first-line consolidation setting</td>
</tr>
<tr>
<td></td>
<td>Not recommended for patients who relapse after first-line therapy and demonstrate sensitive disease after second-line therapy (not BCR inhibitors)</td>
</tr>
<tr>
<td>Richter transformation</td>
<td>Recommended for patients who relapse after first-line therapy, have refractory disease after second-line therapy (not BCR inhibitors), and show an objective response to BCR inhibitors or to a clinical trial</td>
</tr>
<tr>
<td>Purine analogue relapsed and/or refractory disease</td>
<td>Recommended after achieving an objective response to anthracycline-based chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Recommended when there is a lack of response or there is progression after BCL-2 inhibitors</td>
</tr>
<tr>
<td></td>
<td>Not recommended</td>
</tr>
</tbody>
</table>
BCR: B-cell receptor; BCL-2: B-cell lymphoma 2; CLL: chronic lymphocytic leukemia; HCT: hematopoietic cell transplantation.

**National Comprehensive Cancer Network Guidelines**
Current National Comprehensive Cancer Network guidelines (v.2.2019) for CLL and small lymphocytic lymphoma (SLL) state that allogeneic HCT may be considered for patients:

• Without significant comorbidities and CLL refractory to small molecule inhibitor therapy
• With relapsed CLL or SLL and without a 17p deletion or TP53 variant
• With CLL or SLL, a response to treatment, and with a complex karyotype
• With CLL (Rai stages 0-IV) or SLL (Lugano stages II-IV), after histologic transformation to diffuse large B-cell/Hodgkin lymphoma.

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

**Medicare National Coverage**
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing and Unpublished Clinical Trials**
A search of ClinicalTrials.gov in November 2017 did not identify any ongoing or unpublished trials that would likely influence this review.

**REFERENCES**
2. Blue Cross and Blue Shield Association (TEC). High-dose chemotherapy plus allogeneic stem cells to treat chronic lymphocytic leukemia or small lymphocytic lymphoma. TEC Assessments. 2002; Volume 17: Tab 4.


**Billing Coding/Physician Documentation Information**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38204</td>
<td>Management of recipient hematopoietic progenitor cell donor search and cell acquisition</td>
</tr>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogenic</td>
</tr>
<tr>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>38207</td>
<td>Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage</td>
</tr>
<tr>
<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing</td>
</tr>
<tr>
<td>38209</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing</td>
</tr>
<tr>
<td>38210</td>
<td>Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion</td>
</tr>
<tr>
<td>38211</td>
<td>Transplant preparation of hematopoietic progenitor cells; tumor cell depletion</td>
</tr>
<tr>
<td>38212</td>
<td>Transplant preparation of hematopoietic progenitor cells; red blood cell removal</td>
</tr>
<tr>
<td>38213</td>
<td>Transplant preparation of hematopoietic progenitor cells; platelet depletion</td>
</tr>
<tr>
<td>38214</td>
<td>Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion</td>
</tr>
<tr>
<td>38215</td>
<td>Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer</td>
</tr>
<tr>
<td>38220</td>
<td>Bone marrow; aspiration only</td>
</tr>
<tr>
<td>38221</td>
<td>Bone marrow; biopsy, needle or trocar</td>
</tr>
<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</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>Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions</td>
</tr>
<tr>
<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
</tr>
<tr>
<td>S2142</td>
<td>Cord blood-derived stem transplantation, allogeneic</td>
</tr>
<tr>
<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 pre- and post-transplant care in the global definition.</td>
</tr>
</tbody>
</table>

**Additional Policy Key Words**

HSCT
Hematopoietic stem cell transplantation

**Policy Implementation/Update Information**

12/1/01 New policy.
12/1/02 No policy statement changes. Added new codes.
12/1/03  No policy statement changes. Deleted codes.
12/1/04  No policy statement changes. Added new G-codes (G0265, G0266, and G0267). Added statement that this requires prior authorization.
12/1/05  No policy statement changes.
12/1/06  No policy statement changes.
12/1/07  No policy statement changes.
12/1/08  Policy reviewed with literature search and revised extensively; “high-dose chemotherapy” removed from policy title and policy statements. “Stem-cell transplantation” (SCT) now used instead of “stem-cell support” (SCS) in policy and policy statements. Intent of current policy statements unchanged. References 5-9 and 11 added; reference 12 updated.
12/1/09  No policy statement changes.
1/14/10  Interim change. Policy statement regarding allogeneic transplant in patients with markers of poor-risk disease changed; now may be considered medically necessary.

12/1/10  No policy statement changes.
12/1/11  No policy statement changes.
6/1/12  No policy statement changes.
6/1/13  No policy statement changes.
6/1/14  No policy statement changes. Added CPT codes 38230, 38232
6/1/15  No policy statement changes.
6/1/16  “Hematopoietic stem cell transplantation (HSCT)” was replaced with “hematopoietic cell transplantation (HCT)” in the policy statements, title, and text. No policy statement changes.
6/1/17  No policy statement changes.
6/1/18  No policy statement changes.
6/1/19  No policy statement changes.
6/1/20  No policy statement changes.

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