Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

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Replaces: 8.01.514

Policy

Allogeneic hematopoietic cell transplantation is considered medically necessary to treat chronic lymphocytic leukemia or small lymphocytic lymphoma in patients with markers of poor-risk disease (see Policy Guidelines and Rationale sections). 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.

Autologous hematopoietic cell transplantation is considered investigational to treat chronic lymphocytic leukemia or small lymphocytic lymphoma in patients without markers of poor-risk disease.

Related Policies

7.01.50 Placental and Umbilical Cord Blood as a Source of Stem Cells
8.01.529 Hematopoietic Stem-Cell Transplantation for Non-Hodgkin Lymphomas
8.01.532 Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors

Policy Guidelines

Staging and Prognosis of Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia

Two scoring systems are used to determine stage and prognosis of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic leukemia (SLL). As outlined in 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 Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia

<table>
<thead>
<tr>
<th>Rai</th>
<th>Risk</th>
<th>Description</th>
<th>Median</th>
<th>Binet</th>
<th>Description</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td>Survival, ( y )</td>
<td>Stage</td>
<td>Survival, ( y )</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>-------</td>
<td>-----------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Low Lymphocytosis</td>
<td>&gt;10</td>
<td>A ( \leq 3 ) lymphoid areas, normal hemoglobin and platelets</td>
<td>&gt;10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Intermediat e Lymphocytosis + lymphadenopathy</td>
<td>7-9</td>
<td>B ( \geq 3 ) lymphoid areas, normal hemoglobin and platelets</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Intermediat e Lymphocytosis + splenomegaly</td>
<td>7-9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>High Lymphocytosis + anemia ± lymphadenopathy or splenomegaly</td>
<td>1.5-5</td>
<td>C Any number of lymphoid areas, anemia, thrombocytopenia</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>High Lymphocytosis + thrombocytopenia ± anemia, splenomegaly, or lymphadenopathy</td>
<td>1.5-5</td>
<td></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. These are summarized in Table 2, according to availability in clinical centers.

**Table 2. Markers of Poor Prognosis in Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia**

<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 or SLL</td>
<td>- Del(11q22-q23) (loss of ATM gene)</td>
</tr>
<tr>
<td>- Peripheral lymphocyte doubling time &lt;12 mo</td>
<td>- del(17p13)/variant TP53</td>
</tr>
<tr>
<td>- CD38+</td>
<td>- Trisomy 12</td>
</tr>
<tr>
<td>- Elevated ( \beta_2 )-microglobulin level</td>
<td>- Elevated serum CD23</td>
</tr>
<tr>
<td>- Diffuse marrow histology</td>
<td>- Elevated serum tumor necrosis factor-( \alpha )</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; IgVH: immunoglobulin heavy-chain variable-region; SLL: small lymphocytic lymphoma.

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 HCT**

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for reduced-intensity conditioning (RIC) allogeneic HCT. These include those patients whose age (typically >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 before a second allogeneic HCT if a complete remission could be reinduced with chemotherapy.

The ideal allogeneic donors are HLA-identical siblings, matched at the HLA-A, B, and DR loci (6/6). 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. Most 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.
Risk stratification of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) guides therapy decisions, which may include hematopoietic cell transplantation (HCT) 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 poor-risk 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 (e.g., 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 Related Policies.

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 (“classical”) practice of allogeneic HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total-body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that develops after engraftment of allogeneic 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 HCT, 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 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 (CR). 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**

RIC refers to the pre-transplant 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 (TRM) and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor
chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For the purposes of this Policy, the term “reduced-intensity conditioning” will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (conventional) regimens.

Scope

Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

Benefit Application

The following considerations may supersede this policy:

- State mandates requiring coverage for autologous hematopoietic bone marrow transplantation offered as part of clinical trials of autologous bone marrow transplantation approved by the National Institutes of Health (NIH).
- Some plans may participate in voluntary programs offering coverage for patients participating in NIH-approved clinical trials of cancer chemotherapies, including autologous hematopoietic bone marrow transplantation.

Rationale

This policy was created in 1999, and has been updated regularly based on literature searches of the MEDLINE and EMBASE online databases. The latest literature review was conducted through November 9, 2016.

The original review was based on 2 TEC Assessments, one 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 hematopoietic cell transplantation (allo-HCT) to treat CLL and SLL.(2) Both documents 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.

Reviews have discussed 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.(3-8) The conclusions reached in these reviews suggest that, although autologous HCT may prolong survival in select patients with CLL or SLL (e.g., those with chemotherapy-sensitive malignancy who had a good response to front-line therapy and were transplanted early in the course of disease), it has not yet been shown to be curative.

Allogeneic Hematopoietic Cell Transplantation

Data compiled in review articles have suggested that myeloablative allo-HCT has curative potential for CLL or SLL.(6-9) 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.(10) 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 (RIC) 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.(10,11) Six published nonrandomized studies involved a total of 328 patients with advanced CLL who underwent RIC allo-HCT using conditioning regimens that included fludarabine in various combinations including cyclophosphamide, busulfan, rituximab, alemtuzumab, and total body irradiation.(12-17) 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 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 (NRM) 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 of RIC 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 were 23%, 42%, and 65%, respectively. EFS estimates were similar for all genetic subsets, including those with a 17p deletion.

Section Summary

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

A 2015 systematic review of autologous HCT as first-line consolidation in CLL included a literature search through November 2014.(19) 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 [HR], 0.91; 95% confidence interval [CI], 0.62 to 1.33) or in PFS (HR=0.70; 95% CI, 0.32 to 1.52). There was a statistically significant improvement in EFS favoring autologous HCT (HR=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) addressed autologous HCT as second- or third-line treatment of CLL.(20) The trial compared autologous HCT (n=112) and postinduction observation (n=111) for consolidation in patients with CLL who achieved a complete response (CR; 59% of total) or very good partial response (VGPR; 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 was 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 NRM between groups (4% for autologous HCT vs 0% for observation; p=0.33). 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.(21) Two secondary analyses were performed to further investigate the impact of HCT and relapse on QOL. In the primary analysis, the authors demonstrate 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
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 on autologous HCT as second- or third-line treatment of CLL did not find that HCT improved the net health outcome.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in December 2016 did not identify any ongoing or unpublished trials that would likely influence this review.

Summary of Evidence
For individuals who have chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (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 poor-risk 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.

Clinical Input Received 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 2009. Three of 4 reviewers agreed that allogeneic hematopoietic cell transplantation (HCT) was of value to patients with poor-risk chronic lymphocytic leukemia (see Policy Guidelines section), and that this procedure should be medically necessary in this setting. However, the reviewers indicate that the specific approach (e.g., 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 (ASBMT) published guidelines on indications for autologous and allogeneic hematopoietic cell transplantation (allo-HCT) for chronic lymphocytic leukemia (CLL). (22) Recommendations described the current consensus on use of HCT within and outside of the clinical trial setting. Treatment recommendations are shown in Table 3.

Table 3: ASBMT 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>

ASBMT: American Society for Blood and Marrow Transplantation; 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, ASBMT published clinical practice recommendations with additional detail on allo-HCT for CLL. (23) Recommendations are shown in Table 4.

Table 4: ASBMT 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>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>
<td></td>
</tr>
<tr>
<td>Recommended for patients who relapse after first-line therapy, have refractory disease after second-line therapy (including BCR inhibitors but not BCL-2 inhibitors) and show an objective response to BCL-2 inhibitors or to a clinical trial</td>
<td></td>
</tr>
<tr>
<td>Recommended when there is a lack of response or there is progression after BCL-2 inhibitors</td>
<td></td>
</tr>
<tr>
<td>Richter transformation</td>
<td>Recommended after achieving an objective response to anthracycline-based chemotherapy</td>
</tr>
<tr>
<td>Purine analogue relapsed and/or refractory disease</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

ASBMT: American Society for Blood and Marrow Transplantation; 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 (NCCN) guidelines (v.1.2017) for CLL and small lymphocytic lymphoma (SLL) state that allogeneic HCT may be considered for patients (24):
- With relapsed CLL or SLL and without a17p deletion or TP53 mutation
- 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 (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.
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.


Appendix

N/A

History

<table>
<thead>
<tr>
<th>Date</th>
<th>Reason</th>
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<tbody>
<tr>
<td>03/10/14</td>
<td>New Policy. Policy replaces 8.01.514. Policy updated with literature review through December, 2013; reference 11 added. In new policy, policy statement regarding autologous HCT changed from medically necessary to investigational. Policy statement regarding allogeneic HCT changed to medically necessary only in patients with markers of poor-risk disease as defined in Policy Guidelines.</td>
</tr>
<tr>
<td>04/18/14</td>
<td>Update Related Policies. Delete 8.01.20 and replace with 8.01.529.</td>
</tr>
<tr>
<td>06/27/14</td>
<td>Update Related Policies. Remove 8.01.35 and add 8.01.532.</td>
</tr>
<tr>
<td>12/03/14</td>
<td>Update Related Policies. Remove 8.01.17.</td>
</tr>
<tr>
<td>03/10/15</td>
<td>Annual Review. Policy updated with literature review through December 22, 2014; no new references added; no change to policy statements. ICD-9 and ICD-10 diagnosis codes removed; not utilized in adjudication. HCPCS Q and J code ranges removed.</td>
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<tr>
<td>06/14/16</td>
<td>Annual Review. Annual review. Literature review. No change to policy statement.</td>
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<td>11/04/16</td>
<td>Coding update. Removed codes that are transplant benefit related.</td>
</tr>
<tr>
<td>03/14/17</td>
<td>Annual review. Policy updated with literature review through November 9, 2016; references 22-23 added. Policy statements unchanged.</td>
</tr>
</tbody>
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Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2017 Premera All Rights Reserved.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
• Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
• Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5952. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

Arabic (Arabic):
يحتوي هذا الإشعار المعلومات هامة. قد يكون هذا الإشعار معلوماتًا هامة يجب الانتباه إليها. يحتوي هذا الإشعار معلوماتًا هامة يجب الانتباه إليها.

Premera Blue Cross
4631 N.W. Market St.
Seattle, WA 98107

Phone 800-722-1471 (TTY: 800-842-5357)

Oromoo (Cushite):

Deutsche (German):

Italiano (Italian):
This notification contains important information. This notification may contain important information about your application or coverage. Please see Premera Blue Cross at 800-722-1471 (TTY: 800-842-5357) for assistance or to contact us.

Premera Blue Cross

200 N. Columbus
 Olympia, WA 98501

Support Line

We are committed to providing excellent care and service to all customers. If you have questions or need assistance, please contact us at 800-722-1471 (TTY: 800-842-5357).