

| | |
|---|--------------------------------------|
| 8.01.15 Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma | |
| Original Policy Date: January 7, 2011 | Effective Date: April 1, 2022 |
| Section: 11.0 Transplant | Page: Page 1 of 16 |

Policy Statement

Allogeneic hematopoietic cell transplantation may be 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.

The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered **investigational**.

NOTE: Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

Policy Guidelines

The American Society of Transplantation Consensus Conference on the use of hepatitis C viremic donors in solid organ transplantation concluded that the transplantation of organs from HCV viremic donors into HCV-negative recipients should be conducted only under monitored IRB-approved protocols and studies. (See Supplemental Information).

Staging and Prognosis of Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

Two scoring systems are used to determine stage and prognosis of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (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 or Small Lymphocytic Lymphoma

| Rai Stage | Risk | Description | Median Survival, y | Binet Stage | Description | Median Survival, y |
|-----------|--------------|---|--------------------|-------------|--|--------------------|
| 0 | Low | Lymphocytosis | >10 | A | < 3 lymphoid areas, normal hemoglobin and platelets | >10 |
| I | Intermediate | Lymphocytosis + lymphadenopathy | 7 to 9 | B | ≥3 lymphoid areas, normal hemoglobin and platelets | 7 |
| II | Intermediate | Lymphocytosis + splenomegaly/ hepatomegaly ± lymphadenopathy | 7 to 9 | | | |
| III | High | Lymphocytosis + anemia ± lymphadenopathy, hepatomegaly, or splenomegaly | 1.5 to 5 | C | Any number of lymphoid areas, anemia, thrombocytopenia | 5 |

| Rai Stage | Risk | Description | Median Survival, y | Binet Stage | Description | Median Survival, y |
|-----------|------|---|--------------------|-------------|-------------|--------------------|
| IV | High | Lymphocytosis + thrombocytopenia ± anemia, splenomegaly, or lymphadenopathy | 1.5 to 5 | | | |

Because prognoses of patients vary within the different Rai and Binet classifications, other prognostic markers are used in conjunction with staging to determine clinical management.

The National Comprehensive Cancer Network guideline on CLL/SLL stated the following as unfavorable prognostic factors: DNA sequencing with mutated *TP53* or $\leq 2\%$ immunoglobulin heavy-chain variable (*IGHV*) mutation; interphase cytogenetics with del17p or deletion of 11q (del11q); or complex karyotype (≥ 3 unrelated chromosome abnormalities in more than 1 cell on karyotype).

Reduced-Intensity Conditioning for Allogeneic Hematopoietic Cell Transplantation

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered as candidates for reduced-intensity conditioning (RIC) allogeneic hematopoietic cell transplantation (allo-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 score) preclude use of a standard myeloablative conditioning regimen. A patient who relapses following a conventional myeloablative allo-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 allo-HCT if complete remission could be reinduced with chemotherapy.

The ideal allogeneic donors are human leukocyte antigen (HLA)- identical siblings, matched at the HLA-A, -B, and -DR loci on each arm of chromosome 6. Related donors mismatched at a single 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 graft-versus-host disease and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

Coding

CPT centralized codes describing allogeneic and autologous HCT services to the hematology section (CPT 38204-38242). Not all codes are applicable for each stem cell transplant procedure. For example, Plans should determine if cryopreservation is performed. A range of codes describes services associated with cryopreservation, storage, and thawing of cells (38207-38215). The following CPT code describes cryopreservation and storage:

- **38207:** Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage

The following CPT codes describe thawing and washing of cryopreserved cells:

- **38208:** Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
- **38209:** Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor

The following CPT codes describe certain cell types being depleted:

- **38210:** Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
- **38211:** Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
- **38212:** Transplant preparation of hematopoietic progenitor cells; red blood cell removal
- **38213:** Transplant preparation of hematopoietic progenitor cells; platelet depletion
- **38214:** Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion

The following CPT code describes plasma cell concentration:

- **38215:** Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer

Description

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.

Related Policies

- Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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

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 the 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.

Chronic lymphocytic leukemia 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, but can undergo transformation to a more aggressive form of the 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 a 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 an 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 a donor (allogeneic HCT [allo-HCT]). These cells 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).

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 Hematopoietic Cell Transplantation

Conventional Conditioning for Hematopoietic Cell Transplantation

The conventional practice of allo-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 effect that develops after engraftment of allogeneic stem cells within the patient's bone marrow space. The slower graft-versus-malignancy 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 events 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 allo-HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increases the 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 Allogeneic Hematopoietic Cell Transplantation

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 in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of nonrelapse mortality and relapse due to residual disease. Reduced-intensity conditioning regimens can be viewed as a continuum in effects, from near 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.

Literature Review

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 1 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. Randomized controlled trials 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.

Allogeneic Hematopoietic Cell Transplantation

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 PICO was used to select literature to inform this review.

Populations

The relevant population of interest is 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 overall survival (OS), disease-specific survival, change in disease status, treatment-related mortality, and treatment-related morbidity.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Data compiled in review articles through 2012 suggested that myeloablative allo-HCT has curative potential for CLL or SLL.^{1,2,3,4} Long-term disease control (33% to 65% OS at 3 to 6 years) due to a low rate of late recurrences has been observed in all published series, regardless of donor source or conditioning regimen.⁵ However, high rates (24% to 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.^{5,6} Six published nonrandomized studies involved a total of 328 patients with advanced CLL who underwent RIC allo-HCT using regimens that included fludarabine in various combinations including cyclophosphamide, busulfan, rituximab, alemtuzumab, and total body irradiation.^{7,8,9,10,11,12} 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% to 67%) received stem cells from a donor other than a human leukocyte antigen (HLA)-identical sibling. Reported nonrelapse mortality associated primarily with graft-versus-host disease (GVHD) and its complications ranged from 2% at 100 days to 26% overall at median follow-up ranging from 1.7 to 5 years. Overall survival 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 RIC allo-HCT in patients (N=90; median age, 53 years; range, 27 to 65) with poor-risk CLL, defined as having 1 of the following: refractoriness or early relapse (i.e., <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).¹³ With a median follow-up of 46 months, 4-year NRM, event-free survival (EFS), and OS rates were 23%, 42%, and 65%, respectively. Event-free survival estimates were similar for all genetic subsets, including those with a 17p deletion.

Section Summary: Allogeneic Hematopoietic Cell Transplantation

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. 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 Hematopoietic Cell Transplantation

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 PICO was used to select literature to inform this review.

Populations

The relevant population of interest is 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 OS, disease-specific survival, change in disease status, treatment-related mortality, and treatment-related morbidity.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Systematic Review

A 2015 systematic review of autologous HCT as the first-line consolidation in CLL included a literature search through November 2014.¹⁴ 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.

Randomized Controlled Trials

A phase 3 European Intergroup RCT (2011) evaluated autologous HCT as second- or third-line treatment of CLL.¹⁵ 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 to 62 months) in the autograft group and 24 months (range, 17 to 32 months) in the observation group; 5-year EFS rates were 42% and 24%, respectively ($p < .001$). The relapse rate at 5-year follow-up was 54% in the autograft group and 76% in the observational group ($p < .001$); median time to relapse requiring therapy or to death (whichever came first) was 65 months (range, 59 to 71 months) and 40 months (range, 25 to 56 months), respectively ($p = .002$). Overall survival 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 ($p = .77$), with no evidence of a plateau in the areas under the curve. There was no significant difference in nonrelapse mortality between groups (4% for autologous HCT vs. 0% for observation; $p = .33$). 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.¹⁶ 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 Hematopoietic Cell Transplantation

For individuals who have CLL/SLL who receive autologous HCT, the evidence includes RCTs and a systematic review. 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 allogeneic HCT (allo-HCT), the evidence includes single-arm prospective and registry-based studies. 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 an improvement in the net health outcome.

For individuals who have CLL/SLL who receive autologous HCT, the evidence includes randomized controlled trials and a systematic review. 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 that the technology results in an improvement in the net health outcome.

Supplemental Information

The American Society of Transplantation (2017) convened a consensus conference of experts to address issues related to the transplantation of hepatitis C virus (HCV) viremic solid organs into HCV non-viremic recipients.²⁰ Key findings and recommendations are summarized in Table 2.

Table 2. American Society of Transplantation Consensus Conference - Use of HCV Viremic Donors

| | Content Area | Key Point |
|---|----------------------------|--|
| 1 | Definition of HCV positive | HCV –viremic reflecting a positive NAT should be adopted |
| 2 | Data interpretation | HCV antibody status alone limits interpretation of outcomes of transplantation of HCV “positive” organs |
| 3 | Transmission and Treatment | Highest risk for unexpected HCV transmission is associated with organ donation from a person who injected drugs within the eclipse or pre-viremic period |
| 4 | OPTN policy | No current policies prevent transplantation of HCV-viremic organs into HCV non-viremic recipients |
| 5 | Ethical considerations | Transplantation of HCV-viremic organs into HCV non-viremic recipients should be conducted under site specific IRB approved protocols with multi-step informed consent. |

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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.

Clinical input was sought to help determine whether the use of hematopoietic cell transplantation for individuals with chronic lymphocytic leukemia (CLL) would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests from Blue Cross Blue Shield Association, input was received from 1 specialty medical center reviewer, 1 academic medical center reviewer, and 2 Blue Distinction Center reviewers in 2010. Three of 4 reviewers agreed that allogeneic (allo-) hematopoietic cell transplantation (HCT) was of value to patients with poor-risk CLL (see Policy Guidelines section) and that this procedure should be medically necessary for this setting. However, reviewers indicated that the specific approach (e.g., reduced-intensity conditioning vs. myeloablative conditioning) should be individualized based on criteria such as age and health status. For individuals who have CLL who receive autologous HCT, clinical input does not support a clinically meaningful improvement in net health outcome and does not indicate this use is consistent with generally accepted medical practice. All reviewers concurred with the policy statement that autologous HCT is investigational.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society for Blood and Marrow Transplantation

In 2015, the American Society for Blood and Marrow Transplantation published guidelines on indications for allo-HCT and autologous HCT for CLL.¹⁷ Recommendations described the current consensus on the use of HCT in and out of the clinical trial setting. Treatment recommendations are shown in Table 3.

Table 3. 2015 Recommendations for Allogeneic and Autologous Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia

| Adult Indications | Allogeneic HCT | Autologous HCT |
|---------------------------------------|----------------|----------------|
| High-risk, first or greater remission | C | N |
| T cell, prolymphocytic leukemia | R | R |
| B cell, prolymphocytic leukemia | R | R |
| Transformation to high-grade lymphoma | C | C |

C: standard of care, clinical evidence available; 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.¹⁸ Recommendations are shown in Table 4 .

Table 4. 2016 Recommendations for Allogeneic Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia

| Indications | Allogeneic HCT |
|--|--|
| High-risk CLL | Not recommended in the first-line consolidation setting Not recommended for patients who relapse after first-line therapy and demonstrate sensitive disease after second-line therapy (not BCR inhibitors) 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 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 |
| Richter transformation | Recommended when there is a lack of response or there is progression after BCL-2 inhibitors Recommended after achieving an objective response to anthracycline-based chemotherapy |
| Purine analogue relapsed and/or refractory disease | Not recommended |

BCL-2: B-cell lymphoma 2; BCR: B-cell receptor; CLL: chronic lymphocytic leukemia; HCT: hematopoietic cell transplantation.

National Comprehensive Cancer Network Guidelines

Current National Comprehensive Cancer Network guidelines (v.1.2022) for CLL and small lymphocytic lymphoma (SLL) state the following regarding HCT:¹⁹

- "Allogeneic HCT can be considered for CLL/SLL refractory to small-molecule therapy in patients without significant comorbidities."
- "For patients with CLL/SLL with del(17p) or TP53 mutation, a discussion of allogeneic HCT could be considered for patients in remission with or after ibrutinib therapy, if complex karyotype [CK] (≥3 abnormalities) is present. However, available data suggest that CK (≥5 abnormalities) is associated with inferior overall survival [OS] and event-free survival [EFS] following allogeneic HCT with reduced-intensity conditioning in patients with high-risk interphase cytogenetics."
- In patients with histologic transformation (Richter's) and progression, allogeneic HCT can be considered for certain patients with disease responding to initial chemotherapy. In addition, "autologous HCT may also be appropriate for patients with disease responding to initial therapy but who are not candidates for allogeneic HCT due to age, comorbidities, or lack of a suitable donor."

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 2021 did not identify any ongoing or unpublished trials that would likely influence this review.

References

1. Gine E, Moreno C, Esteve J, et al. The role of stem-cell transplantation in chronic lymphocytic leukemia risk-adapted therapy. *Best Pract Res Clin Haematol*. Sep 2007; 20(3): 529-43. PMID 17707838
2. Gribben JG. Role of allogeneic hematopoietic stem-cell transplantation in chronic lymphocytic leukemia. *J Clin Oncol*. Oct 20 2008; 26(30): 4864-5. PMID 18794537
3. Kharfan-Dabaja MA, Anasetti C, Santos ES. Hematopoietic cell transplantation for chronic lymphocytic leukemia: an evolving concept. *Biol Blood Marrow Transplant*. Apr 2007; 13(4): 373-85. PMID 17382245
4. Gladstone DE, Fuchs E. Hematopoietic stem cell transplantation for chronic lymphocytic leukemia. *Curr Opin Oncol*. Mar 2012; 24(2): 176-81. PMID 22234253
5. Delgado J, Milligan DW, Dreger P. Allogeneic hematopoietic cell transplantation for chronic lymphocytic leukemia: ready for prime time?. *Blood*. Sep 24 2009; 114(13): 2581-8. PMID 19641189
6. Dreger P. Allotransplantation for chronic lymphocytic leukemia. *Hematology Am Soc Hematol Educ Program*. 2009: 602-9. PMID 20008245
7. Brown JR, Kim HT, Li S, et al. Predictors of improved progression-free survival after nonmyeloablative allogeneic stem cell transplantation for advanced chronic lymphocytic leukemia. *Biol Blood Marrow Transplant*. Oct 2006; 12(10): 1056-64. PMID 17084369
8. Delgado J, Thomson K, Russell N, et al. Results of alemtuzumab-based reduced-intensity allogeneic transplantation for chronic lymphocytic leukemia: a British Society of Blood and Marrow Transplantation Study. *Blood*. Feb 15 2006; 107(4): 1724-30. PMID 16239425
9. Dreger P, Brand R, Hansz J, et al. Treatment-related mortality and graft-versus-leukemia activity after allogeneic stem cell transplantation for chronic lymphocytic leukemia using intensity-reduced conditioning. *Leukemia*. May 2003; 17(5): 841-8. PMID 12750695
10. Khouri IF, Saliba RM, Admirand J, et al. Graft-versus-leukaemia effect after non-myeloablative haematopoietic transplantation can overcome the unfavourable expression of ZAP-70 in refractory chronic lymphocytic leukaemia. *Br J Haematol*. May 2007; 137(4): 355-63. PMID 17456058
11. Schetelig J, Thiede C, Bornhauser M, et al. Evidence of a graft-versus-leukemia effect in chronic lymphocytic leukemia after reduced-intensity conditioning and allogeneic stem-cell transplantation: the Cooperative German Transplant Study Group. *J Clin Oncol*. Jul 15 2003; 21(14): 2747-53. PMID 12860954
12. Sorrow ML, Storer BE, Sandmaier BM, et al. Five-year follow-up of patients with advanced chronic lymphocytic leukemia treated with allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. *J Clin Oncol*. Oct 20 2008; 26(30): 4912-20. PMID 18794548
13. Dreger P, Dohner H, Ritgen M, et al. Allogeneic stem cell transplantation provides durable disease control in poor-risk chronic lymphocytic leukemia: long-term clinical and MRD results of the German CLL Study Group CLL3X trial. *Blood*. Oct 07 2010; 116(14): 2438-47. PMID 20595516
14. Reljic T, Kumar A, Djulbegovic B, et al. High-dose therapy and autologous hematopoietic cell transplantation as front-line consolidation in chronic lymphocytic leukemia: a systematic review. *Bone Marrow Transplant*. Aug 2015; 50(8): 1144. PMID 26242579
15. Michallet M, Dreger P, Sutton L, et al. Autologous hematopoietic stem cell transplantation in chronic lymphocytic leukemia: results of European intergroup randomized trial comparing autografting versus observation. *Blood*. Feb 03 2011; 117(5): 1516-21. PMID 21106985
16. de Wreede LC, Watson M, van Os M, et al. Improved relapse-free survival after autologous stem cell transplantation does not translate into better quality of life in

- chronic lymphocytic leukemia: lessons from the randomized European Society for Blood and Marrow Transplantation-Intergroup study. *Am J Hematol*. Feb 2014; 89(2): 174-80. PMID 24123244
17. Majhail NS, Farnia SH, Carpenter PA, et al. Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. Nov 2015; 21(11): 1863-1869. PMID 26256941
 18. Kharfan-Dabaja MA, Kumar A, Hamadani M, et al. Clinical Practice Recommendations for Use of Allogeneic Hematopoietic Cell Transplantation in Chronic Lymphocytic Leukemia on Behalf of the Guidelines Committee of the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. Dec 2016; 22(12): 2117-2125. PMID 27660167
 19. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: chronic lymphocytic leukemia/small lymphocytic lymphoma. Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed November 29, 2021.
 20. Levitsky J, Formica RN, Bloom RD, et al. The American Society of Transplantation Consensus Conference on the Use of Hepatitis C Viremic Donors in Solid Organ Transplantation. *Am J Transplant*. Nov 2017;17(11):2790-2802. PMID 28556422

Documentation for Clinical Review

Please provide the following documentation:

- Referring physician history and physical
- Bone marrow transplant consultation report and/or progress notes documenting:
 - Diagnosis (including disease staging) and prognosis
 - Synopsis of alternative treatments performed and results
 - Specific transplant type being requested
- Surgical consultation report and/or progress notes
- Results of completed transplant evaluation including:
 - Clinical history including comorbidities
 - Specific issues identified during the transplant evaluation
 - Consultation reports/letters (when applicable)
 - Correspondence from referring physicians (when applicable)
 - Identification of donor for allogeneic related bone marrow/stem cell transplant (when information available)
- Medical social service/social worker and/or psychiatric (if issues are noted) evaluations including psychosocial assessment or impression of patient's ability to be an adequate candidate for transplant
- Radiology reports including:
 - Chest x-ray (CXR)
 - PET scan, CT scan and bone survey (as appropriate)
- Cardiology procedures and pulmonary function reports:
 - EKG
 - Echocardiogram
 - Pulmonary function tests (PFTs)
- Biopsy/Pathology reports including:
 - Bone marrow biopsy
 - Lymph node biopsy (as appropriate)
- Laboratory reports

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

| Type | Code | Description |
|-------|-------|---|
| CPT® | 38204 | Management of recipient hematopoietic progenitor cell donor search and cell acquisition |
| | 38205 | Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic |
| | 38206 | Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous |
| | 38207 | Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage |
| | 38208 | Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor |
| | 38209 | Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor |
| | 38210 | Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion |
| | 38211 | Transplant preparation of hematopoietic progenitor cells; tumor cell depletion |
| | 38212 | Transplant preparation of hematopoietic progenitor cells; red blood cell removal |
| | 38213 | Transplant preparation of hematopoietic progenitor cells; platelet depletion |
| | 38214 | Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion |
| | 38215 | Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer |
| | 38220 | Diagnostic bone marrow; aspiration(s) |
| | 38221 | Diagnostic bone marrow; biopsy(ies) |
| | 38222 | Diagnostic bone marrow; biopsy(ies) and aspiration(s) |
| | 38230 | Bone marrow harvesting for transplantation; allogeneic |
| | 38232 | Bone marrow harvesting for transplantation; autologous |
| | 38240 | Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor |
| | 38241 | Hematopoietic progenitor cell (HPC); autologous transplantation |
| | 38242 | Allogeneic lymphocyte infusions |
| HCPCS | S2140 | Cord blood harvesting for transplantation, allogeneic |
| | S2142 | Cord blood-derived stem-cell transplantation, allogeneic |
| | S2150 | 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 |

| Type | Code | Description |
|------|------|---|
| | | outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and posttransplant care in the global definition |

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

| Effective Date | Action |
|----------------|--|
| 01/07/2011 | BCBSA Medical Policy adoption |
| 04/30/2015 | Policy revision with position change |
| 06/01/2016 | Policy revision with position change |
| 03/01/2017 | Policy title change from Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma Policy revision without position change |
| 01/01/2018 | Coding update |
| 03/01/2018 | Policy revision without position change |
| 03/01/2019 | Policy revision without position change |
| 11/01/2019 | Policy revision without position change |
| 04/01/2020 | Annual review. No change to policy statement. Literature review updated. |
| 03/01/2021 | Annual review. No change to policy statement. Policy guidelines and literature updated. |
| 04/01/2022 | Annual review. No change to policy statement. Policy guidelines and literature updated. |

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an

authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

| POLICY STATEMENT | |
|--|--|
| BEFORE Red font: Verbiage removed | AFTER Blue font: Verbiage Changes/Additions |
| <p>Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma 8.01.15</p> <p>Policy Statement: 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.</p> <p>Autologous hematopoietic cell transplantation is considered investigational to treat chronic lymphocytic leukemia or small lymphocytic lymphoma.</p> <p>The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered investigational.</p> | <p>Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma 8.01.15</p> <p>Policy Statement: Allogeneic hematopoietic cell transplantation may be 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.</p> <p>Autologous hematopoietic cell transplantation is considered investigational to treat chronic lymphocytic leukemia or small lymphocytic lymphoma.</p> <p>The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered investigational.</p> |