Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 9/1/24**
(See policy history boxes for previous effective dates)

Title: BMT/Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma – Autologous or Allogeneic

Description/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 two years. Although typically responsive to initial therapy, CLL and SLL are rarely cured by conventional therapy, and nearly all patients ultimately die of their disease. This natural 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 “naïve” 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 a critical factor for achieving a good outcome of allogeneic 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

Myeloablative (Conventional) Conditioning

The myeloablative (conventional) practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation. Intense conditioning regimens are limited to individuals whose health status is sufficient to tolerate the administration of cytotoxic agents with total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self-immunologic effector cells. While the slower GVM effect is considered the potentially curative component, it may be overwhelmed by substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host-disease, which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow with presumably normal hematopoietic stem cells obtained from the individual before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the individual’s disease is in complete remission. Individuals who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

Reduced-Intensity or Non-myeloablative Conditioning for Allo-HCT

Reduced-intensity conditioning (RIC), sometimes referred to as non-myeloablative (NMA) conditioning, refers to the pretransplant use of lower doses of cytotoxic drugs with or without less intense regimens of radiotherapy than are used in myeloablative conditioning treatments. Although the definition of RIC/NMA is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse

mortality. The goal of RIC/NMA is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. These RIC/NMA regimens range from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and individual condition. Individuals who undergo RIC/NMA with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism.

Policy Guidelines

STAGING AND PROGNOSIS OF CHRONIC LYMPHOCYTIC LEUKEMIA OR SMALL LYMPHOCYTIC LYMPHOMA

Two scoring systems are used to determine stage and prognosis of individuals with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). As outlined in the Table PG1, the Rai and Binet staging systems classify individuals into 3 risk groups with different prognoses and are used to make therapeutic decisions.

Table PG1. Rai and Binet Classification for CLL or SLL

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	Int	Lymphocytosis + lymphadenopathy	7-9	B	≥3 lymphoid areas, normal hemoglobin and platelets	7
II	Int	Lymphocytosis + splenomegaly/ hepatomegaly± lymphadenopathy	7-9			
III	High	Lymphocytosis + anemia ± lymphadenopathy, hepatomegaly or splenomegaly	1.5-5	C	Any number of lymphoid areas, anemia, thrombocytopenia	5
IV	High	Lymphocytosis + thrombocytopenia ± anemia, splenomegaly, or lymphadenopathy	1.5-5			

Int: Intermediate

Because prognoses of individuals vary 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 PG2, according to availability in clinical centers.

Table PG2. Markers of Poor Prognosis in CLL or SLL

Community Center	Specialized Center
• Advanced Rai or Binet stage	• IgVh wild type
• Male sex	• Expression of ZAP-70 protein
• Atypical morphology or CLL or SLL	• Del(11q22-q23) (loss of *ATM* genet)
• Peripheral lymphocyte doubling time <12 mo.	• del(17p13)/variant *TP53*
• CD38-positive	• Trisomy 12
• Elevated b_2-microglobulin level	• Elevated serum CD23
• Diffuse marrow histology	• Elevated serum tumor necrosis factor-α
• Elevated serum lactate dehydrogenase level	• Elevated serum thymidine kinase

• Fludarabine resistance

CLL: chronic lymphocytic leukemia; IgVh: immunoglobulin heavy-chain variable-region; SLL: small lymphocytic lymphoma.

The National Comprehensive Cancer Network guideline on CLL/SLL stated the following as unfavorable prognostic factors: DNA sequencing with mutated TP53 or ≤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 HCT

Some individuals for whom a conventional myeloablative allotransplant could be curative may be considered candidates for reduced intensity conditioning (RIC) allogeneic hematopoietic cell transplantation (allo-HCT). These include those individuals whose age (typically >60 years) or co-morbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen. An individual 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 individual would likely undergo RIC prior to a second allo-HCT if a complete remission could be re-induced 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 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 individual - with whom usually there is sharing of only three of the six major histocompatibility antigens have been under investigation as a stem cell source. Most individuals 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.

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.

Medical Policy Statement

The safety and effectiveness of *allogeneic* hematopoietic cell transplantation have been established. It may be considered a useful therapeutic option for individuals meeting specific selection criteria.

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

Inclusionary and Exclusionary Guidelines

Inclusions:
For *allogeneic* hematopoietic cell transplantation, the individual must have

- Chronic lymphocytic leukemia or small cell lymphocytic leukemia **AND**
- Markers of poor-risk disease (see Table PG2).

Use of a myeloablative or reduced-intensity pre-transplant conditioning regimen should be individualized based on factors that include patient age, the presence of co-morbidities, and disease burden.

Exclusions:
Autologous hematopoietic cell transplantation for CLL or SLL.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes: *(for allogenic transplant)*

38204	38205	38207	38208	38209	38210
38211	38212	38213	38214	38215	38230
38240	38242	81267	81268	81370	81371
81372	81373	81374	81375	81376	81377
81378	81379	81380	81381	81382	81383
86812	86813	86816	86817	86821	86822
S2140	S2142	S2150			

Other codes (investigational, not medically necessary, etc.)(For autologous transplant): *(The italicized codes would be considered experimental/investigational if done with an autologous transplant)*

38204	*38205*	*38206*	*38207*	*38208*	*38209*
38210	*38211*	*38212*	*38213*	*38214*	*38215*
38220	*38221*	38232	38241	*81267*	*81268*
81370	*81371*	*81372*	*81373*	*81374*	*81375*
81376	*81377*	*81378*	*81379*	*81380*	*81381*
86812	*86813*	*86816*	*86817*	*86821*	*86822*
S2150					

POTENTIAL CONTRAINDICATIONS FOR TRANSPLANT:

Note: Final patient eligibility for transplant is subject to the judgment and discretion of the requesting transplant center.

The selection process for approved tissue transplants is designed to obtain the best result for each patient. Therefore, relative contraindications to HCT may include, but are not limited to:

- Poor cardiac function: Ejection fraction should be greater than 45% with no overt symptoms of congestive heart failure.
- Poor pulmonary function: Pulmonary function tests must be greater than or equal to 50% of predicted value.
- Poor renal function: Renal creatinine clearance should be greater than 40 ml/min or creatinine must be less than or equal to 2mg/dl.
- Poor liver function: There should be no history of severe chronic liver disease
- Presence of HIV or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus (HTLV-1).

Clinical documentation supplied to the health plan must demonstrate that attending staff at the transplant center have considered all contraindications as part of their overall evaluation of potential organ transplant recipient and have decided to proceed.

Rationale

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

The following PICO was used to select literature to inform this review.

Clinical Context and Therapy Purpose
The purpose of allogeneic and/or autologous HCT in individuals 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.

Populations
The relevant populations of interest are individuals with CLL or SLL and markers of poor-risk disease.

Interventions
The therapy being considered is allogeneic and/or 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 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.

ALLOGENEIC HCT

Review of Evidence

Data compiled in review articles have suggest that myeloablative allogeneic HCT has curative potential for CLL or SLL.(1-4) Long-term disease control (33-65% 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 (24-47%) of treatment-related mortality (TRM) discourage this approach in early or lower-risk disease, particularly among older patients whose health status typically precludes the use of myeloablative conditioning.

The development of reduced-intensity conditioning (RIC) regimens has extended the use of allo-HCT to older or less fit patients who account for the larger proportion of this disease than younger patients, as outlined in several recent review articles.(5,6) 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.(7-12) Most patients in these series were heavily pretreated, with a median 3-5 courses of prior regimens. Among individual studies, 27-57% of patients had chemotherapy-refractory disease, genetic abnormalities including del 17p13, del 11q22, and VH unmutated, or a combination of those characteristics. A substantial proportion in each study (18-67%) received stem cells from a donor other than an HLA-identical sibling. Reported non-relapse mortality (NRM), associated primarily with graft-versus-host disease (GVHD) and its complications, ranged from 2% at 100 days to 26% overall at median follow-up that ranged from 1.7 years to 5 years. Overall survival rates ranged from 48-70% at follow-up that ranged from 2-5 years. Similar results were reported for progression-free survival (PFS), which was 34-58% at 2–5-year follow-up. Similar results were for progression-free survival (PFS), 34-58% at 2–5-year follow-up. Very similar results were reported from a Phase II study published in 2010 of RIC allo-HCT in patients (n=90; median age 53 years, range: 27-65 years) with poor-risk CLL, defined as having 1 of the following: refractoriness or early relapse (i.e., <12 months) after purine-analog therapy; relapse after autologous HCT; or, progressive disease in the presence of an unfavorable genetic marker (11q or 17p deletion, and/or unmutated IgVh 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 were 23%, 42%, and 65%, respectively. EFS was similar for all genetic subsets, including those with a 17p deletion mutation.

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 HCT

Systemic Review
A 2015 systematic review of autologous HCT as front-line consolidation in CLL included a literature search through November 2014.(14) Four RCTs in adult patients were included in the review. Outcomes included OS, PFS, EFS, and harms (adverse events, treatment-related mortality and secondary malignancies). In these 4 trials, 301 patients were randomized to the autologous HCT arm and 299 to the control arm using front-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.

Randomized Controlled Trials
A phase III European Intergroup RCT (2011) addressed autologous HCT as second- or third-line treatment of CLL.(15) The trial compared autologous HSCT (n=112) and post-induction 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 31-65 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 observed group; the 5-year EFS was 42% and 24%, respectively ($p<0.001$). The relapse rate at five-year follow-up was 54% in the autograft group versus 76% in the observational group ($p<0.001$); median time to relapse requiring therapy or to death (whichever came first) was 65 months (range: 59-71 months) and 40 months (range: 25-56 months), respectively ($p=0.002$). Overall survival probability at 5-year follow-up was 86% (95% confidence interval [CI]: 77-94%) in the autograft arm and 84% (95% CI: 75-93%) 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% in the autologous HCT group vs 0% in the observation group $p=0.33$). Myelodysplastic syndrome (MDS) was observed at follow-up in 3 patients receiving an autograft and in 1 patient in the observational group.

In a subsequent 2014, authors of the European Intergroup RCT presented quality-of-life (QOL) findings from this trial.(16) 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 two years after randomization.

Section Summary: Autologous HCT
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 on 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 chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) and markers of poor-risk disease who receive 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 suggests 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) and systematic reviews. 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 suggests 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 outcomes.

Supplemental Information

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.

Blue Cross Blue Shield Association (BCBSA) sought clinical input 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, BCBSA received input from 1 specialty medical center reviewer, 1 academic medical center reviewer, and 2 Blue Distinction Center reviewers while this policy was under review. Three of

4 reviewers agree that allo-HCT was of value in patients who have poor-risk CLL (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., RIC versus 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 concur with the policy statement that autologous HCT is investigational.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Society for Blood Marrow and Transplantation

The American Society for Blood and Marrow Transplantation (2015) published guidelines on indications for autologous and allogeneic hematopoietic cell transplantation (allo-HCT) for chronic lymphocytic leukemia (CLL).(17) Recommendations described the current consensus on use of HCT within and outside of the clinical trial setting. Treatment recommendations are shown in Table 1.

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

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; 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.(18) Recommendations are shown in Table 2.

Table 2. 2016 Recommendations for Allogeneic HCT for CLL

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
	Recommended when there is a lack of response or there is progression after BCL-2 inhibitors
Richter transformation	Recommended after achieving an objective response to anthracycline-based chemotherapy
Purine analogue relapsed and/or refractory disease	Not recommended

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

American Society for Transplantation and Cellular Therapy

In 2020, the American Society for Transplantation and Cellular Therapy (ASTCT) published guidelines on indications for HCT and immune effector cell therapy.(19) Recommendations for CLL are shown in Table 4.

Table 4. 2020 Recommendations for Allogeneic Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia

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

C: standard of care, clinical evidence available; HCT: hematopoietic cell transplantation; N: not generally recommended; R: standard of care, rare indication; S: standard of care

National Comprehensive Cancer Network Guidelines

Current National Comprehensive Cancer Network (NCCN) guidelines for CLL and small lymphocytic lymphoma (SLL) state the following regarding HCT:(20)

- "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.

Government Regulations

National:

Medicare National Coverage Determinations Manual 100-03, Chapter 1, Part 2, Section 110.23, "Stem Cell Transplantation." Effective date: 1/27/16; Implementation Date: 10/3/16; Manual updated: 11/30/18

General

Stem cell transplantation is a process in which stem cells are harvested from either a patient's (autologous) or donor's (allogeneic) bone marrow or peripheral blood for intravenous infusion. Autologous stem cell transplantation (AuSCT) is a technique for restoring stem cells using the patient's own previously stored cells. AuSCT must be used to effect hematopoietic reconstitution following severely myelotoxic doses of chemotherapy (HDCT) and/or radiotherapy used to treat various malignancies. Allogeneic hematopoietic stem cell transplantation (HSCT) is a procedure in which a portion of a healthy donor's stem cell or bone marrow is obtained and prepared for intravenous infusion. Allogeneic HSCT may be used to restore function in recipients having an inherited or acquired deficiency or defect. Hematopoietic stem cells are multi-potent stem cells that give rise to all the blood cell types;

these stem cells form blood and immune cells. A hematopoietic stem cell is a cell isolated from blood or bone marrow that can renew itself, differentiate to a variety of specialized cells, can mobilize out of the bone marrow into circulating blood, and can undergo programmed cell death, called apoptosis - a process by which cells that are unneeded or detrimental will self-destruct.

The Centers for Medicare & Medicaid Services (CMS) is clarifying that bone marrow and peripheral blood stem cell transplantation is a process which includes mobilization, harvesting, and transplant of bone marrow or peripheral blood stem cells and the administration of high dose chemotherapy or radiotherapy prior to the actual transplant. When bone marrow or peripheral blood stem cell transplantation is covered, all necessary steps are included in coverage. When bone marrow or peripheral blood stem cell transplantation is non-covered, none of the steps are covered.

Indications and Limitations of Coverage

A. Nationally Covered Indications

I. Allogeneic Hematopoietic STEM CELL Transplantation (HSCT)
   a) Effective for services performed on or after August 1, 1978, for the treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary

Other

All other indications for STEM CELL TRANSPLANTATION not otherwise noted above as covered or non-covered remain at local Medicare Administrative Contractor discretion.

(This NCD last reviewed January 2016.)

Local:

No Local determination available.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- BMT – Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia
- BMT – Hematopoietic Cell Transplantation for Acute Myeloid Leukemia
- BMT – Hematopoietic Cell Transplantation for Autoimmune Diseases
- BMT – Hematopoietic Cell Transplantation for Chronic Myelogenous Leukemia
- BMT – Hematopoietic Cell Transplantation for CNS Embryonal Tumors and Ependymoma
- BMT – Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer
- BMT – Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias
- BMT – Hematopoietic Cell Transplantation for Hodgkin Lymphoma

- BMT – Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
- BMT – Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
- BMT – Hematopoietic Cell Transplantation for Primary Amyloidosis
- BMT – Hematopoietic Cell Transplantation for Solid Tumors of Childhood
- BMT – Hematopoietic Cell Transplantation for Treatment of Multiple Myeloma
- BMT – Hematopoietic Cell Transplantation for Waldenström's Macroglobulinemia
- BMT – Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors
- BMT – Malignant Astrocytoma and Gliomas, Autologous
- Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant
- Orthopedic Applications of Stem-Cell Therapy (Including Allografts and Bone Substitutes used with Autologous Bone Marrow)

References

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 4/4/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/12	7/30/12	7/30/12	Joint policy established
3/1/14	12/10/13	1/6/14	Routine update. No change in policy status.
9/1/15	6/19/15	7/16/15	Routine update. No change in policy status.
9/1/16	6/21/16	6/21/16	Routine update. No change in policy status.
9/1/17	6/20/17	6/20/17	Routine maintenance
9/1/18	6/19/18	6/19/18	Routine maintenance
9/1/19	6/18/19		Routine maintenance
9/1/20	6/16/20		Routine maintenance
9/1/21	6/15/21		Routine maintenance
9/1/22	6/21/22		Routine maintenance
9/1/23	6/13/23		Routine maintenance (slp) Vendor managed: N/A
9/1/24	6/11/24		Routine maintenance (slp) Vendor managed: N/A

Next Review Date: 2nd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: BMT/HEMATOPOIETIC CELL TRANSPLANTATION FOR CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA – AUTOLOGOUS OR ALLOGENEIC

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.