Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia

Policy # 00053
Original Effective Date: 01/28/2002
Current Effective Date: 06/10/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia is addressed separately in medical policy 00428.

Note: Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas is addressed separately in medical policy 00062.

Note: Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms is addressed separately in medical policy 00061.

Note: Hematopoietic Cell Transplantation for Acute Myeloid Leukemia is addressed separately in medical policy 00049.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider allogeneic hematopoietic cell transplantation (allo-HCT) using a myeloablative conditioning regimen as a treatment of chronic myeloid leukemia (CML) to be **eligible for coverage.****

Based on review of available data, the Company may consider allogeneic hematopoietic cell transplantation (allo-HCT) using a reduced-intensity conditioning (RIC) regimen as a treatment of chronic myeloid leukemia (CML) in individuals who meet clinical criteria for an allo-HCT, but who are not considered candidates for a myeloablative conditioning allo-HCT, to be **eligible for coverage.****

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When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers autologous hematopoietic cell transplantation as a treatment of chronic myeloid leukemia (CML) to be **investigational.***

Policy Guidelines

Some individuals for whom a conventional myeloablative allotransplant could be curative may be considered candidates for reduced-intensity conditioning allogeneic hematopoietic cell transplantation. They include those individuals whose age (typically >60 years) or comorbidities (eg, liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status score) preclude use of a standard myeloablative conditioning regimen.

For individuals who qualify for a myeloablative allogeneic hematopoietic cell transplantation on the basis of clinical status, either a myeloablative or a reduced-intensity conditioning regimen may be considered medically necessary.

Background/Overview

Chronic Myeloid Leukemia

Chronic myeloid leukemia (CML) is a hematopoietic stem cell disorder characterized by the presence of a chromosomal abnormality called the Philadelphia chromosome, which results from a reciprocal translocation between the long arms of chromosomes 9 and 22. This cytogenetic change results in constitutive activation of the fusion gene BCR-ABL, a tyrosine kinase that stimulates unregulated cell proliferation, inhibits cell apoptosis, creates genetic instability, and upsets interactions between CML cells and the bone marrow stroma only in malignant cells. The disease accounts for about 15% of newly diagnosed cases of leukemia in adults and occurs in 1 to 2 cases per 100,000 adults.

The natural history of the disease consists of an initial (indolent) chronic phase, lasting a median of 3 years, which typically transforms into an accelerated phase, followed by a “blast crisis,” which is

usually the terminal event. Most patients present in chronic phase, often with nonspecific symptoms secondary to anemia and splenomegaly. A diagnosis is based on the presence of the Philadelphia chromosome abnormality by routine cytogenetics, or by detection of abnormal BCR-ABL products by fluorescence in situ hybridization or molecular studies, in the setting of persistent unexplained leukocytosis. Conventional dose chemotherapy regimens used for chronic phase disease can induce multiple remissions and delay the onset of blast crisis to a median of 4 to 6 years. However, successive remissions are invariably shorter and more difficult to achieve than their predecessors.

Treatment
Historically, the only curative therapy for CML in blast phase has been allogeneic hematopoietic cell transplantation (allo-HCT), which was used more widely earlier in the disease process given the lack of other therapies for chronic phase CML. Drug therapies for chronic phase CML were limited to nonspecific agents including busulfan, hydroxyurea, and interferon-α.

Imatinib mesylate (Gleevec®‡), a selective inhibitor of the abnormal BCR-ABL tyrosine kinase protein, is considered the treatment of choice for newly diagnosed CML. While imatinib can be highly effective in suppressing CML, it is not curative and is ineffective in 20% to 30% of patients, initially or due to development of *BCR-ABL* variants that cause resistance to the drug. Even so, the overall survival of patients who present in the chronic phase is greater than 95% at 2 years and 80% to 90% at 5 years.

For CML, 2 other tyrosine kinase inhibitors ([TKIs]; dasatinib, nilotinib) have received marketing approval from the U.S. Food and Drug Administration (FDA) as first-line therapies or following failure or patient intolerance of imatinib. Three additional TKIs (bosutinib, ponatinib, asciminib) have been approved for use in patients resistant or intolerant to prior therapy.

For patients on imatinib who have disease progression, the therapeutic options include increasing the imatinib dose, changing to another TKI, or allo-HCT. Detection of *BCR-ABL* variants may be important in determining an alternative TKI; the presence of the *T315I* variant is associated with resistance to all TKIs and should indicate the need for allo-HCT or experimental therapy. Tyrosine kinase inhibitors have been associated with long-term remissions; however, if disease progression occurs on TKI therapy, allo-HCT is generally indicated and offers the potential for cure.

Hematopoietic Cell Transplantation
Hematopoietic cell transplantation is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune function in cancer patients who receive bone marrow-toxic doses of cytotoxic drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allo-HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allo-HCT, immunologic compatibility between donor and patient is a critical factor for achieving a successful outcome. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. Human leukocyte antigen refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. An acceptable donor will match the patient at all or most of the HLA loci.

Conditioning for Hematopoietic Cell Transplantation

Conventional Conditioning
The conventional ("classical") practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without 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 the initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by 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 potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits

subsequent engraftment and repopulation of the bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation
Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the clinical definition of RIC 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 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. Reduced-intensity conditioning regimens range from nearly total 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. In this review, the term *reduced-intensity conditioning* will refer to all conditioning regimens intended to be nonmyeloablative.

FDA or Other Governmental Regulatory Approval

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

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical

practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Description

Chronic myeloid leukemia (CML) is a hematopoietic stem cell disorder characterized by the presence of a chromosomal abnormality called the Philadelphia chromosome, which results from a reciprocal translocation between the long arms of chromosomes 9 and 22. Chronic myeloid leukemia most often presents in a chronic phase from which it progresses to an accelerated and then a blast phase. Allogeneic hematopoietic cell transplantation (allo-HCT) is a treatment option for CML.

Summary of Evidence

For individuals who have chronic myeloid leukemia (CML) who receive allogeneic hematopoietic cell transplantation (allo-HCT), the evidence includes systematic reviews, randomized controlled trials (RCTs), and multiple prospective and retrospective series. Relevant outcomes are overall survival (OS), disease-specific survival (DSS), and treatment-related morbidity and mortality. The introduction of tyrosine kinase inhibitors (TKIs) has significantly changed the clinical use of hematopoietic cell transplantation (HCT) for CML. Tyrosine kinase inhibitors have replaced HCT as initial therapy for patients with chronic phase CML. However, a significant proportion of cases fail to respond to TKIs, develop a resistance to them, or cannot tolerate TKIs and proceed to allo-HCT. Also, allo-HCT represents the only potentially curative option for those patients in accelerated or blast phase CML. Currently, available evidence has suggested that TKI pretreatment does not lead to worse outcomes if HCT is needed. Myeloablative conditioning (MAC) regimens before HCT are used in younger (<60 years) patients without significant comorbidities. However, for patients with more comorbidities and/or more advanced age for whom MAC regimens would be prohibitively high-risk, evidence has suggested that reasonable outcomes can be obtained after HCT. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have CML who receive autologous HCT, the evidence includes case series. Relevant outcomes are OS, DSS, and treatment-related morbidity and mortality. In the largest series (N=200 patients), median survival was 36 months for patients transplanted during an accelerated phase; median survival data were not available for patients transplanted in chronic phase. Controlled studies are needed to permit conclusions on the impact of autologous HCT on health outcomes in

patients with CML. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

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 Transplantation and Cellular Therapy

In 2020, the guidelines by the American Society for Transplantation and Cellular Therapy (formerly the American Society for Blood and Marrow Transplantation) addressed indications for autologous and allogeneic hematopoietic cell transplantation (allo-HCT) for chronic myeloid leukemia (CML). Recommendations are listed in Table 1.

Table 1. Recommendations on Allogeneic and Autologous HCT for CML

Indications	Allogeneic HCT	Autologous HCT
Pediatric		
Chronic phase	C	N
Accelerated phase	C	N
Blast phase	C	N
Adult		
Chronic phase, tyrosine kinase inhibitor intolerant	C	N
Chronic phase, tyrosine kinase inhibitor refractory	C	N
Chronic phase 2+	S	N

Accelerated phase	S	N
Blast phase	S	N

C: standard of care, clinical evidence available, CML: chronic myeloid leukemia; HCT: hematopoietic cell transplantation; N: not generally recommended; S: standard of care.

National Comprehensive Cancer Network

National Comprehensive Cancer Network CML guidelines (v.1.2024) recommend allo-HCT as an alternative treatment only for high-risk settings or in patients with advanced phase CML. Relevant recommendations are:

- "Allogeneic HCT is no longer recommended as a first-line treatment option for CP [chronic phase]-CML."
- "Allogeneic HCT is an appropriate treatment option for the very rare patients presenting with BP [blast phase]-CML at diagnosis, patients with disease that is resistant to TKIs [tyrosine kinase inhibitors], patients with progression to AP [accelerated phase]-CML or BP-CML while on TKI therapy, and patients with CML that is resistant and/or intolerant to all TKIs "
- "...Evaluation for allogeneic HCT is recommended for all patients with AP-CML or BP-CML"

Autologous HCT for CML is not addressed in these guidelines.

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

Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03314974	Myeloablative Allogeneic Hematopoietic Cell Transplantation Using a Related or Unrelated Donor for the Treatment of Hematological Diseases	300	Nov 2025
Unpublished			
NCT01760655	A Two Step Approach to Reduced Intensity Allogeneic Hematopoietic Stem Cell Transplantation for High Risk Hematologic Malignancies	62	Dec 2022

NCT: national clinical trial.

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Policy History

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12/06/2001	Medical Policy Committee review
03/25/2002	Managed Care Advisory Council approval
06/24/2002	Format revision. No substance change to policy.
05/07/2004	Medical Director review
05/18/2004	Medical Policy Committee review. Format revision. High-Dose Chemotherapy and Hematopoietic Stem Cell Support for Treatment of Chronic Myelogenous Leukemia policy developed separately from current HDC with Hematopoietic Stem Cell Support policy. No substance change to policy.
06/28/2004	Managed Care Advisory Council approval
06/07/2005	Medical Director review
06/21/2005	Medical Policy Committee review. Policy revised to consider eligibility for autologous SCS cases where no allogeneic donor match is available and patient has undergone treatment with Gleevec.
07/15/2005	Managed Care Advisory Council approval
07/07/2006	Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
07/11/2007	Medical Director review
07/18/2007	Medical Policy Committee approval. Rationale updated. Coverage eligibility unchanged.
10/01/2008	Medical Director review
10/22/2008	Medical Policy Committee approval. Autologous stem cell transplants are now considered investigational.

10/01/2009	Medical Policy Committee review
10/14/2009	Medical Policy Implementation Committee approval. No change to coverage eligibility.
10/14/2010	Medical Policy Committee review
10/20/2010	Medical Policy Implementation Committee approval. Coverage eligibility updated.
10/06/2011	Medical Policy Committee review
10/19/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/11/2012	Medical Policy Committee review
10/31/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/04/2013	Coding updated
10/03/2013	Medical Policy Committee review
10/16/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/07/2015	Medical Policy Committee review
05/20/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
05/05/2016	Medical Policy Committee review
05/18/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
05/04/2017	Medical Policy Committee review
05/17/2017	Medical Policy Implementation Committee approval. “Stem” removed from title and policy statements.
05/03/2018	Medical Policy Committee review
05/16/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Policy Guidelines moved from the coverage section to the Policy Guidelines section.
05/02/2019	Medical Policy Committee review
05/15/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

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05/07/2020	Medical Policy Committee review
05/13/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/06/2021	Medical Policy Committee review
05/12/2021	Medical Policy Implementation Committee approval. Revised investigational statement and replaced "allogeneic" with "autologous" for hematopoietic cell transplantation as a treatment of chronic myeloid leukemia.
05/05/2022	Medical Policy Committee review
05/11/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/04/2023	Medical Policy Committee review
05/10/2023	Medical Policy Implementation Committee approval. Replaced "patients" with "individuals" in the coverage section. Coverage eligibility unchanged.
05/02/2024	Medical Policy Committee review
05/08/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 05/2025

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38230, 38232, 38240, 38241, 38242, 38243
HCPCS	S2140, S2142, S2150
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: 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 eligibility for coverage.