

Corporate Medical Policy

Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia

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Description of Procedure or Service

Chronic Myeloid Leukemia

Chronic myeloid leukemia (CML) is a hematopoietic stem-cell disorder that is characterized by the presence of a chromosomal abnormality called the Philadelphia chromosome, which results from reciprocal translocation between the long arms of chromosomes 9 and 22. This cytogenetic change results in constitutive activation of BCR-ABL, a tyrosine kinase (TK) that stimulates unregulated cell proliferation, inhibition of apoptosis, genetic instability, and perturbation of the interactions between CML cells and the bone marrow stroma only in malignant cells. CML accounts for about 15% of newly diagnosed cases of leukemia in adults and occurs in about 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 that 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 that are secondary to anemia and splenomegaly. CML is diagnosed 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 4–6 years. However, successive remissions are invariably shorter and more difficult to achieve than their predecessors. Historically the only curative therapy for CML in blast phase was HCT, and HCT 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-alpha.

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

Two other TK inhibitors (TKIs, dasatinib, nilotinib) have received marketing approval from the U.S. Food and Drug Administration (FDA) to treat CML as front line therapy or following failure or patient intolerance of imatinib. Two additional TKIs, bosutinib and ponatinib, have been approved for use in patients resistant or intolerant to prior therapy.

For patients who progress on imatinib, the therapeutic options include increasing the imatinib dose, changing to another TKI, or all-HSCT. Detection of BCR-ABL mutations may be important

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in determining an alternative TKI; the presence of T315/mutation is associated with resistance to all TKIs and should indicate need for allo-HCT or an experimental therapy. TKIs have been associated with long-term remissions; however, if progression occurs on TKI therapy, allo-HCT is generally indicated and offers the potential for cure.

Hematopoietic Cell Transplantation

Hematopoietic cell transplantation (HCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole body radiation therapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic 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.

Conventional Preparative Conditioning for HCT

The conventional (“classical”) practice of allogeneic HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that develops after engraftment of allogeneic stem cells within the patient’s bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HSCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections. The immune reactivity between donor T cells and malignant cells that is responsible for the GVM effect also leads to acute and chronic GVHD.

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 prior to 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 prior to engraftment, but not GVHD.

Reduced-Intensity Conditioning for Allogeneic HCT

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose

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myeloablative conditioning treatments. The goal of RIC is not only to reduce disease burden, but also to minimize as much as possible associated treatment-related morbidity and nonrelapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HSCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For the purposes of this Policy, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

For CML, RIC regimens were initially used to extend the use of allo-HCT to the estimated 70% of CML patients who were ineligible for myeloablative conditioning regimens because of advanced age or comorbidities. The use of RIC and allo-HCT is of particular interest for treatment of CML, given the relatively pronounced susceptibility of this malignancy to the graft-versus-leukemia (GVL) effect of allogeneic hematopoietic progenitor cells following their engraftment in the host.

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

If the medical criteria and guidelines are not met, some patients may be eligible for coverage under clinical trials. Refer to the policy, Clinical Trial Services.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

Some health benefit plans may exclude benefits for transplantation.

When Hematopoietic Cell Transplant for Chronic Myeloid Leukemia is covered

Allogeneic cell transplantation using a myeloablative conditioning regimen may be considered medically necessary as a treatment of chronic myeloid leukemia (see Policy Guidelines).

Allogeneic hematopoietic cell transplantation using a reduced-intensity conditioning (RIC) regimen may be considered medically necessary as a treatment of chronic myeloid leukemia in patients who meet clinical criteria for an allogeneic HCT but who are not considered candidates for a myeloablative conditioning allogeneic HCT.

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When Hematopoietic Cell Transplant for Chronic Myeloid Leukemia is not covered

Autologous cell transplantation is considered investigational as a treatment of chronic myeloid leukemia. BCBSNC does not provide coverage for investigational services or procedures.

Policy Guidelines

Refer to the individual member's benefit plan for prior review requirements.

Chronic myeloid leukemia (CML) is a hematopoietic stem cell disorder that is characterized by the presence of a chromosomal abnormality called the Philadelphia chromosome, which results from reciprocal translocation between the long arms of chromosomes 9 and 22. CML 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.

For individuals who have CML who receive allo-HCT, the evidence includes systematic reviews, randomized controlled trials (RCTs), and multiple prospective and retrospective series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The introduction of tyrosine kinase inhibitors (TKIs) has significantly changed the clinical use of HCT for CML. TKIs have replaced HCT as initial therapy for patients with chronic phase CML. However, a significant proportion of cases fails to respond to TKIs, develops resistance to them, or patients cannot tolerate TKIs and proceed to allo-HCT. In addition, allo-HCT represents the only potentially curative option for those patients in the 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 regimens prior to HCT are used in younger (<60 years) patients without significant comorbidities. However, for patients with more comorbidities and/or more advanced age for whom myeloablative conditioning 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 a meaningful improvement in the net health outcome.

For individuals who have CML who receive autologous HCT, the evidence includes case series. Relevant outcomes are overall survival, disease-specific survival, 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 the effects of the technology on health outcomes.

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for reduced-intensity conditioning allogeneic hematopoietic cell transplantation (HCT). They include those patients 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 patients who qualify for a myeloablative allogeneic HCT on the basis of clinical status, either a myeloablative or reduced-intensity conditioning regimen may be considered medically necessary.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative

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Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 38205, 38206, 38230, 38232, 38240, 38241, 38242, 38243, S2150

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Bone Marrow Transplant for Chronic Myelogenous Leukemia

BCBSA Medical Policy Reference Manual, 12/1/1999

The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, Centennial Edition, Section 11, Hematology and Oncology, Chapter 138, Leukemias. www.merck.com

BCBSA Medical Policy Reference Manual, 10/8/2002; 8.01.30

Specialty Matched Consultant Advisory Panel - 11/2002

National Comprehensive Cancer Network. (2003). NCCN practice guidelines in oncology, chronic myelogenous leukemia. Retrieved 9/7/2004 from http://www.nccn.org/physician_gls/PDF/cml.pdf.

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.30, 7/15/2004

Specialty Matched Consultant Advisory Panel - 11/2004

National Comprehensive Cancer Network. (2006). NCCN practice guidelines in oncology, chronic myelogenous leukemia. Retrieved 8/7/2006 from http://www.nccn.org/physician_gls/PDF/cml.pdf.

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.30, 9/27/2005

Specialty Matched Consultant Advisory Panel - 11/2006

National Comprehensive Cancer Network. (2008). NCCN practice guidelines in oncology, chronic myelogenous leukemia. Retrieved 9/17/2008 from http://www.nccn.org/professionals/physician_gls/PDF/cml.pdf

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.30, 6/12/2008

Specialty Matched Consultant Advisory Panel - 11/2008

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BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.30, 12/10/2009

Medical Director – 8/2010

Specialty Matched Consultant Advisory Panel - 11/2010

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BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.30, 6/9/2011

Specialty Matched Consultant Advisory Panel - 11/2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.30, 12/8/11

Specialty Matched Consultant Advisory Panel - 12/2012

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.30, 12/13/12

Specialty Matched Consultant Advisory Panel – 11/2013

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.30, 12/12/13

Specialty Matched Consultant Advisory Panel – 11/2014

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.30, 12/11/14

Specialty Matched Consultant Advisory Panel – 11/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.30, 1/14/16

Specialty Matched Consultant Advisory Panel – 11/2016

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BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.30, 1/12/17

Medical Director review 1/2017

Specialty Matched Consultant Advisory Panel – 11/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.30, 2/8/18

Specialty Matched Consultant Advisory Panel – 11/2018

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.30, 1/17/19

Specialty Matched Consultant Advisory Panel – 11/2019

Medical Director review 11/2019

Policy Implementation/Update Information

Bone Marrow Transplant for Chronic Myelogenous Leukemia

1/01 Specialty Matched Consultant Advisory Group.

2/01 Original policy issued.

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- 2/03 Specialty Matched Consultant Advisory Panel review 11/2002. No change in criteria. Codes 86812-86822 removed; codes 38231 and 86915 deleted and codes 38242, 38205 and 38206 added to the Billing/Coding section. System coding changes.
- 1/04 Benefits Application and Billing/Coding sections updated for consistency.
- 2/04 Individual CPT codes listed for CPT code ranges 38240-38242 under Billing/Coding section.
- 7/29/04 HCPCS code S2150 added to Billing/Coding section.
- 12/9/04 Specialty Matched Consultant Advisory Panel review 11/29/04. No changes to criteria. Revised Description of Procedure or Service section. Revised wording in When Bone Marrow Transplant for Chronic Myelogenous Leukemia is covered section. Added rationale to Policy Guidelines section. Added policy number to Policy Key Words. "Hematopoietic" and "Opportunistic" added to Definitions. References added.
- 12/11/06 Specialty Matched Consultant Advisory Panel review 11/6/06. Added the following statement to the "Policy" section; "If the medical criteria and guidelines are not met, some patients may be eligible for coverage under clinical trials. Refer to the policy, Clinical Trial Services for Life-Threatening Conditions." References added.
- 12/22/08 Specialty Matched Consultant Advisory Panel review 11/13/2008. No change to policy statement. References added. (btw)
- 6/22/10 Policy Number(s) removed. (amw)

Hematopoietic Stem-Cell Transplantation for Chronic Myelogenous Leukemia

- 9/14/10 Policy name changed from Bone Marrow Transplant for Chronic Myelogenous Leukemia. "Description" section completely revised. Removed statement under "Benefit Application" indicating that "Services for or related to the search for a donor are not covered." Changed wording in the "When Covered" section to indicate; "Allogeneic stem-cell transplantation using a myeloablative conditioning regimen may be considered medically necessary as a treatment of chronic myelogenous leukemia (see Policy Guidelines). Allogeneic HSCT using a reduced-intensity conditioning (RIC) regimen may be considered medically necessary as a treatment of chronic myelogenous leukemia in patients who meet clinical criteria for an allogeneic HSCT but who are not considered candidates for a myeloablative conditioning allogeneic HSCT." Updated "Policy Guidelines" section. References updated. (btw)
- 1/4/11 Specialty Matched Consultant Advisory Panel review 11/29/2010. No change to policy statement. (btw)
- 1/10/12 Specialty Matched Consultant Advisory Panel review 11/30/2011. No change to policy statement. References added. (btw)
- 2/21/12 New 2012 CPT code, 38232, added to Billing/Coding section. (btw)
- 4/17/12 Reference added. (btw).

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- 12/28/12 Specialty Matched Consultant Advisory Panel 12/4/12. No change to policy intent. Added new 2013 CPT code, 38243 to Billing/Coding section. (btw)
- 2/12/13 Reference added. (btw)
- 12/10/13 Specialty Matched Consultant Advisory Panel review 11/20/2013. Updated Policy Guidelines. No change to policy intent. (btw)
- 2/25/14 Reference added. (btw)
- 12/9/14 Specialty Matched Consultant Advisory Panel review 11/24/2014. No change to policy intent. (lpr)
- 2/10/15 Updated the Description section. Reference added. (lpr)
- 12/30/15 Specialty Matched Consultant Advisory Panel review 11/18/2015. No change to policy statement. (lpr)
- 4/1/16 Updated Description and Policy Guidelines sections. No change to policy intent. Reference added. (lpr)
- 12/30/16 Specialty Matched Consultant Advisory panel review 11/30/2016. No change to policy intent. (lpr)

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- 4/28/17 Policy title changed from “Hematopoietic Stem Cell Transplantation for Chronic Myelogenous Leukemia” to Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia.” Description and Policy Guidelines sections revised. Reference added. No change to policy intent. Medical Director review 1/2017. (lpr)
- 12/15/17 Specialty Matched Consultant Advisory Panel review 11/29/2017. No change to policy statement. (lpr)
- 1/15/19 Specialty Matched Consultant Advisory Panel review 11/2018. Reference added. No change to policy statement. (lpr)
- 12/10/19 Specialty Matched Consultant Advisory Panel review 11/20/2019. Reference added. No change to policy statement. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.