MASSACHUSETTS

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Medical Policy

Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia

Table of Contents

Policy Number: 212

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Related Policies

- Placental and Umbilical Cord Blood as a Source of Stem Cells, #285
- Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas, #143
- Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms, #155
- Hematopoietic Cell Transplantation for Acute Myeloid Leukemia, #150

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue[SM] and Medicare PPO Blue[SM] Members

Allogeneic hematopoietic cell transplantation (HCT) using a myeloablative conditioning regimen may be considered **MEDICALLY NECESSARY** as a treatment of chronic myeloid leukemia.

Allogeneic HCT using a reduced-intensity conditioning 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.

Note: 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.

Autologous HCT is **INVESTIGATIONAL** as a treatment of chronic myeloid leukemia.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is **required**.
Commercial PPO and Indemnity	Prior authorization is **required**.
Medicare HMO Blue℠	Prior authorization is **required**.
Medicare PPO Blue℠	Prior authorization is **required**.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

CPT codes:	Code Description
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor

HCPCS Codes

HCPCS codes:	Code Description
S2140	Cord blood harvesting for transplantation; allogeneic
S2142	Cord blood derived stem-cell transplantation, allogeneic
S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

ICD-10 Procedure Codes

ICD-10-PCS procedure codes:	Code Description
30233X1	Transfusion of Nonautologous Cord Blood Stem Cells into Peripheral Vein, Percutaneous Approach
30233Y1	Transfusion of Nonautologous Hematopoietic Stem Cells into Peripheral Vein, Percutaneous Approach
30243X1	Transfusion of Nonautologous Cord Blood Stem Cells into Central Vein, Percutaneous Approach

30243Y1	Transfusion of Nonautologous Hematopoietic Stem Cells into Central Vein, Percutaneous Approach
30263X1	Transfusion of Nonautologous Cord Blood Stem Cells into Central Artery, Percutaneous Approach
30263Y1	Transfusion of Nonautologous Hematopoietic Stem Cells into Central Artery, Percutaneous Approach

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. 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. CML accounts for about 15% of newly diagnosed cases of leukemia in adults and occurs in 1 to 2 cases per 100000 adults.[1]

The natural history of the disease consists of an initial (indolent) chronic phase, lasting a median of three 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. CML 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 four to six 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.[1]

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.[2]

For CML, two other tyrosine kinase inhibitors ([TKIs]; dasatinib, nilotinib) have received marketing approval from the U.S. Food and Drug Administration as first-line therapies or following failure or patient intolerance of imatinib. Two additional TKIs (bosutinib, ponatinib) 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. TKIs 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

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

(allo-HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naive” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD). Cord blood is discussed in greater detail in policy #285.

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 with allo-HCT. Compatibility is established by typing of human leukocyte antigens (HLAs) 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 (except umbilical cord blood).

Conventional Conditioning for HCT

The conventional practice of allo-HCT involves administration of cytotoxic agents (eg, cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability 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 that is mediated by non-self-immunologic effector cells that develop after engraftment of allogeneic stem cells within the patient’s bone marrow space. While the slower GVM effect is considered 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 allo-HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increase susceptibility 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 before undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed 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 Allo-HCT

RIC refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiotherapy than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden and to minimize as much as possible associated treatment-related morbidity and nonrelapse mortality 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 nonrelapse mortality and relapse due to residual disease. RIC 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, RIC will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

For CML, RIC regimens were initially administered to extend the use of allo-HCT to the estimated 70% of CML patients ineligible for myeloablative conditioning regimens because of advanced age or comorbidities. The use of RIC and allo-HCT are of particular interest for the treatment of CML, given the

relatively pronounced susceptibility of this malignancy to the graft-versus-leukemia effect of allogeneic hematopoietic progenitor cells following their engraftment in the host.

Summary

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. 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, and multiple prospective and retrospective series. The 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 fail to respond to TKIs, develops 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 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 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 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. The 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.

Policy History

Date	Action
3/2019	BCBSA National medical policy review. Description, summary and references updated. Policy statements unchanged.
1/2019	Outpatient prior authorization is required for all commercial products including Medicare Advantage. Effective 1/1/2019.
3/2018	New references added from BCBSA National medical policy. Background and summary clarified.
2/2018	Clarified coding information.
3/2017	BCBSA National medical policy review. Title changed. Myelogenous changed to myeloid. New references added. 3/1/2017
3/2016	New references added from BCBSA National medical policy.
9/2015	Clarified coding information.
6/2014	Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.
3/2014	New references added from BCBSA National medical policy.
11/2011-4/2012	Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.
7/2011	Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements.
9/2010	Reviewed - Medical Policy Group - Hematology and Oncology.

	No changes to policy statements.
8/1/2010	New policy, effective 8/1/2010, describing covered and non-covered indications.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References

1. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2014 update on diagnosis, monitoring, and management. Am J Hematol. May 2014;89(5):547-556. PMID 24729196
2. Pavlu J, Szydlo RM, Goldman JM, et al. Three decades of transplantation for chronic myeloid leukemia: what have we learned? Blood. Jan 20 2011;117(3):755-763. PMID 20966165
3. Gratwohl A, Pfirrmann M, Zander A, et al. Long-term outcome of patients with newly diagnosed chronic myeloid leukemia: a randomized comparison of stem cell transplantation with drug treatment. Leukemia. Mar 2016;30(3):562-569. PMID 26464170
4. Fernandez HF, Kharfan-Dabaja MA. Tyrosine kinase inhibitors and allogeneic hematopoietic cell transplantation for chronic myeloid leukemia: targeting both therapeutic modalities. Cancer Control. Apr 2009;16(2):153-157. PMID 19337201
5. Apperley JF. Managing the patient with chronic myeloid leukemia through and after allogeneic stem cell transplantation. Hematology Am Soc Hematol Educ Program. Nov 2006:226-232. PMID 17124065
6. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med. Dec 7 2006;355(23):2408-2417. PMID 17151364
7. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. Jun 17 2010;362(24):2260-2270. PMID 20525995
8. Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med. Jun 17 2010;362(24):2251-2259. PMID 20525993
9. Liu YC, Hsiao HH, Chang CS, et al. Outcome of allotransplants in patients with chronic-phase chronic myeloid leukemia following imatinib failure: prognosis revisited. Anticancer Res. Oct 2013;33(10):4663-4667. PMID 24123046
10. Xu L, Zhu H, Hu J, et al. Superiority of allogeneic hematopoietic stem cell transplantation to nilotinib and dasatinib for adult patients with chronic myelogenous leukemia in the accelerated phase. Front Med. Sep 2015;9(3):304-311. PMID 26100855
11. Zhang GF, Zhou M, Bao XB, et al. Imatinib mesylate versus allogeneic hematopoietic stem cell transplantation for patients with chronic myelogenous leukemia. Asian Pac J Cancer Prev. Nov 2016;17(9):4477-4481. PMID 27797264
12. Shen K, Liu Q, Sun J, et al. Prior exposure to imatinib does not impact outcome of allogeneic hematopoietic transplantation for chronic myeloid leukemia patients: a single-center experience in China. Int J Clin Exp Med. May 2015;8(2):2495-2505. PMID 25932195
13. Chamseddine AN, Willekens C, De Botton S, et al. Retrospective study of allogeneic hematopoietic stem cell transplantation in Philadelphia chromosome-positive leukemia: 25 years' experience at Gustave Roussy Cancer Campus. Clin Lymphoma Myeloma Leuk. Jun 2015;15 Suppl:S129-140. PMID 26297265
14. Nair AP, Barnett MJ, Broady RC, et al. Allogeneic hematopoietic stem cell transplantation is an effective salvage therapy for patients with chronic myeloid leukemia presenting with advanced disease or failing treatment with tyrosine kinase inhibitors. Biol Blood Marrow Transplant. Aug 2015;21(8):1437-1444. PMID 25865648
15. Piekarska A, Gil L, Prejzner W, et al. Pretransplantation use of the second-generation tyrosine kinase inhibitors has no negative impact on the HCT outcome. Ann Hematol. Nov 2015;94(11):1891-1897. PMID 26220759

16. Zhao Y, Luo Y, Shi J, et al. Second-generation tyrosine kinase inhibitors combined with stem cell transplantation in patients with imatinib-refractory chronic myeloid leukemia. Am J Med Sci. Jun 2014;347(6):439-445. PMID 24553398
17. Egan DN, Beppu L, Radich JP. Patients with Philadelphia-positive leukemia with BCR-ABL kinase mutations before allogeneic transplantation predominantly relapse with the same mutation. Biol Blood Marrow Transplant. Jan 2015;21(1):184-189. PMID 25300870
18. Chakrabarti S, Buyck HC. Reduced-intensity transplantation in the treatment of haematological malignancies: current status and future-prospects. Curr Stem Cell Res Ther. May 2007;2(2):163-188. PMID 18220901
19. Crawley C, Szydlo R, Lalancette M, et al. Outcomes of reduced-intensity transplantation for chronic myeloid leukemia: an analysis of prognostic factors from the Chronic Leukemia Working Party of the EBMT. Blood. Nov 1 2005;106(9):2969-2976. PMID 15998838
20. Szatrowski TP. Progenitor cell transplantation for chronic myelogenous leukemia. Semin Oncol. Feb 1999;26(1):62-66. PMID 10073562
21. Bhatia R, Verfaillie CM, Miller JS, et al. Autologous transplantation therapy for chronic myelogenous leukemia. Blood. Apr 15 1997;89(8):2623-2634. PMID 9108379
22. McGlave PB, De Fabritiis P, Deisseroth A, et al. Autologous transplants for chronic myelogenous leukaemia: results from eight transplant groups. Lancet. Jun 11 1994;343(8911):1486-1488. PMID 7911185
23. Podesta M, Piaggio G, Sessarego M, et al. Autografting with Ph-negative progenitors in patients at diagnosis of chronic myeloid leukemia induces a prolonged prevalence of Ph-negative hemopoiesis. Exp Hematol. Feb 2000;28(2):210-215. PMID 10706077
24. Meloni G, Capria S, Vignetti M, et al. Ten-year follow-up of a single center prospective trial of unmanipulated peripheral blood stem cell autograft and interferon-alpha in early phase chronic myeloyd leukemia. Haematologica. Jun 2001;86(6):596-601. PMID 11418368
25. Boiron JM, Cahn JY, Meloni G, et al. Chronic myeloid leukemia in first chronic phase not responding to alpha-interferon: outcome and prognostic factors after autologous transplantation. EBMT Working Party on Chronic Leukemias. Bone Marrow Transplant. Aug 1999;24(3):259-264. PMID 10455363
26. McBride NC, Cavenagh JD, Newland AC, et al. Autologous transplantation with Philadelphia-negative progenitor cells for patients with chronic myeloid leukaemia (CML) failing to attain a cytogenetic response to alpha interferon. Bone Marrow Transplant. Dec 2000;26(11):1165-1172. PMID 11149726
27. Michallet M, Thiebaut A, Philip I, et al. Late autologous transplantation in chronic myelogenous leukemia with peripheral blood progenitor cells mobilized by G-CSF and interferon-alpha. Leukemia. Dec 2000;14(12):2064-2069. PMID 11187894
28. Pigneux A, Faberes C, Boiron JM, et al. Autologous stem cell transplantation in chronic myeloid leukemia: a single center experience. Bone Marrow Transplant. Aug 1999;24(3):265-270. PMID 10455364
29. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Chronic Myeloid Leukemia. Version 1.2019. https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf. Accessed January 19, 2019.
30. 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