Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 1/1/13**
(See policy history boxes for previous effective dates)

Title: BMT - Hematopoietic Stem-Cell Transplantation for Chronic Myelogenous Leukemia

Description / Background

Hematopoietic Stem-Cell Transplantation
Hematopoietic stem-cell transplantation (HSCT) 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 HSCT) or from a donor (allogeneic HSCT). 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 HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. 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.

Conventional Preparative Conditioning for HSCT
The conventional (“classical”) practice of allogeneic HSCT 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 success of autologous HSCT 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 HSCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

Reduced-Intensity Conditioning for Allogeneic HSCT

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden but also to minimize as much as possible associated treatment-related morbidity and non-relapse 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 non-myeloablative, as opposed to fully myeloablative (conventional) regimens.

Chronic Myelogenous Leukemia

Chronic myelogenous 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.

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. Conventional-dose 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.

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. Two other TK inhibitors (TKIs, dasatinib, nilotinib) have received marketing approval from the U.S. Food and Drug Administration (FDA) to treat CML following failure or patient intolerance of imatinib. In any case, allogeneic HSCT remains the only treatment capable of inducing durable remissions or cure in CML patients.

Regulatory Status:

N/A

Medical Policy Statement

The safety and effectiveness of allogeneic hematopoietic stem-cell transplantation for chronic myelogenous leukemia have been established. It may be considered a useful therapeutic option in specified situations.

Autologous hematopoietic stem-cell transplantation for chronic myelogenous leukemia is considered experimental/investigational. It has not been scientifically demonstrated to improve health outcomes.

Contraindications

Absolute and relative contraindications represent situations where proceeding with transplant may not be advisable in the context of limited organ/tissue availability. Contraindications may evolve over time as transplant experience grows in the medical community. 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 recipients and have decided to proceed.

Relative contraindications:

The selection process for approved tissue transplants is designed to obtain the best result for each patient. Therefore, relative contraindications to HSCT 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).

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions:
Allogeneic hematopoietic stem-cell transplantation may be considered an established therapeutic option for chronic myelogenous leukemia in the following situations:

- *Allogeneic* hematopoietic stem-cell transplantation using a myeloablative conditioning regimen.
- *Allogeneic* hematopoietic stem-cell transplantation using a reduced-intensity conditioning (RIC) regimen in patients who meet clinical criteria for an allogeneic HSCT but who are not considered candidates for a myeloablative conditioning allogeneic HSCT.

Exclusions:

- *Autologous* hematopoietic stem-cell transplantation as a treatment of chronic myelogenous leukemia.
- All other situations not specified in the inclusions.

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:

38204	38205	38208	38209	38210	38211
38212	38213	38214	38215	38220	38221
38230	38240	S2140	S2142	S2150	

Other codes (investigational, not medically necessary, etc.):

38206	38232	38241

Rationale

Allogeneic HSCT
Allogeneic hematopoietic stem-cell transplantation (HSCT) is the only known potentially curative therapy for chronic myelogenous leukemia (CML). It became a standard of treatment for CML in the 1980s when the graft-versus-leukemia (GVL) effect was shown to be the critical factor for long-term disease control. (1) Studies in patients with chronic phase disease who received a human leukocyte antigen (HLA)-matched sibling donor transplant had a 45–75% probability of long-term disease-free survival, while those transplanted with more advanced disease had a 15–40% long-term survival. (2) Young, good-risk patients transplanted early in the chronic phase from HLA-matched but unrelated donors had a 40–60% probability of long-term survival, although it is lower than that of similar patients transplanted from matched sibling donors. (3, 4)

CML was once the most common malignancy for which allogeneic HSCT was performed, but by 2005, it was in eighth place among hematologic transplantation indications. A retrospective analysis of data from the Center for International Blood and Marrow Transplant Research Center (CIBMTR) showed that transplantation for CML was in decline prior to FDA approval of imatinib in 2001. (5) Subsequently, long-term follow-up results from the International Randomized Study of Interferon and STI 571 (IRIS) of imatinib mesylate, plus the availability of two additional approved TKI agents (nilotinib and dasatinib), have caused modification of the timing of application of allogeneic HSCT. (6-8) This procedure now is typically delayed in patients with newly diagnosed CML, who will receive imatinib mesylate as front-line treatment. It also may only be used early when a complete molecular response to the drug fails or is not achieved soon after starting imatinib administration.

Allogeneic HSCT has continued to develop, with important advancements in the use of nonmyeloablative or reduced-intensity conditioning (RIC) preparative regimens. RIC regimens were initially conceptualized as a means to extend the use of allogeneic HSCT 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 allogeneic HSCT is of particular interest for treatment of CML given the relatively pronounced susceptibility of this malignancy to the GVL effect of allogeneic hematopoietic progenitor cells following their engraftment in the host. Overall, among 9 studies compiled in a recent review, outcomes achieved with RIC allogeneic transplants have been similar to those with conventional allotransplants, with overall survival (OS) rates ranging from 35% at 2.5 years to 85% at 5 years among patients in chronic phase 1 at transplant. (9) Among the studies included in this review, treatment-related mortality or nonrelapse mortality (NRM) ranged from 0% at 1 year to 29% at 1 year. In the largest experience, a retrospective European Group for Blood and Marrow Transplantation (EMBT) study of 186 patients, OS was 54% at 3 years using a variety of RIC regimens in patients in chronic phase 1 (n=118), chronic phase 2 (n=26), acute phase (n=30), and blast crisis (n=12). (10) Among patients transplanted in the first chronic phase (CP1), OS was 69% at 3 years.

RIC regimens have many of the same limitations as standard-intensity conditioning: relapse, graft-versus-host disease (GVHD) (particularly chronic GVHD), and mortality from treatment-related causes other than myelotoxicity. However, in the absence of prospective, comparative, randomized trials, only indirect comparisons can be made between the relative clinical benefits and harms associated with myeloablative and RIC regimens with allogeneic HSCT.

Comparison of study results is further compromised by heterogeneity among patients, treatments, and outcome measures. Nonetheless, clinical evidence suggests outcomes in CML are similar with myeloablative and RIC allogeneic HSCT. (6, 9, 10) Thus, RIC allogeneic HSCT should be considered medically necessary for CML patients who would otherwise be expected to benefit from an allogeneic HSCT.

The advent of tyrosine kinase inhibitor (TKI) therapy has altered the treatment paradigm for CML such that the majority of patients are treated initially with a TKI until disease progresses. While progression may occur within months of starting a TKI, this may be delayed for years, as shown by the results of the IRIS trial (8) and other studies. (6, 7) With the addition of two other TKIs (nilotinib and dasatinib) plus the possibility of effective dose escalation with imatinib to override resistance, it is possible to maintain a typical CML patient past the upper age limit (usually 50-55 years) at which a myeloablative allogeneic HSCT is considered an option. (8, 11, 12) These patients would be eligible for a RIC allogeneic HSCT.

Clinical guidelines and recommendations for management of patients with CML in the context of TKI therapy and allogeneic HSCT have been published. (13-17) They are in concordance with this policy.

Autologous HSCT

A major limitation in the use of autologous HSCT in patients with CML is a high probability that leukemic cells will be infused back into the patient. However, it is recognized that many CML patients still have normal marrow stem cells. Techniques used to isolate and expand this normal clone of cells have included ex vivo purging, long-term culture, and immunophenotype selection. (18) Even without such techniques, there have been isolated case reports of partial cytogenetic remissions after autologous HSCT, and one study has suggested that patients undergoing such therapy may have improved survival compared with historical controls. (2)

Another article summarized the results of 200 consecutive autologous transplants using purged or unpurged marrow from 8 different transplant centers. (19) Of the 200 patients studied, 125 were alive at a median follow-up of 42 months. Of the 142 transplanted in chronic phase, the median survival had not been reached at the time of publication, while the median survival was 35.9 months for those transplanted during an accelerated phase. Other data consist of small, single institution case series using a variety of techniques to enrich the population of normal stem cells among the harvested cells. (2) Additional reports of small, uncontrolled studies with a total of 182 patients (range: 15–41 patients) given autotransplants for CML included patient populations that varied across the studies. Some focused on newly diagnosed patients or those in the first year since diagnosis. (20, 21) Others focused on patients who did not respond to or relapsed after initial treatment using interferon alfa. (22, 23)

Finally, some focused on patients transplanted in the late chronic phase (24) or after transformation to accelerated phase or blast crisis. (25) Although some patients achieved complete or partial molecular remissions and long-term disease-free survival, these studies do not permit conclusions free from the influence of patient selection bias. All autotransplanted patients included in these reports were treated before imatinib mesylate or newer TKIs became available. Since these agents have been shown to induce major hematologic and, less often, cytogenetic remissions, even among patients in accelerated phase and blast crisis, future studies of autotransplants for CML may focus on patients who fail or become resistant to imatinib mesylate. Alternatively, it may be incorporated into combination regimens used for high-dose therapy. (26)

Summary

There has been a significant change in clinical transplantation practice for CML patients, particularly over the past decade subsequent to commercial introduction of three TKI agents: imatinib, dasatinib, and nilotinib. (17) The TKIs have replaced allogeneic HSCT as initial therapy in patients with chronic phase CML. (15) However a significant proportion of cases fail to respond to TKIs, develop resistance to them, or become unable to tolerate all TKIs and go on to allogeneic HSCT. Allogeneic HSCT represents the only potentially curative option for those patients in accelerated or blast phase. (16) Given the successes seen with TKIs in chronic phase CML, and the risks associated with myeloablative autologous HSCT, the latter has declined in use to the extent that few anecdotal reports have been published since the TKI era began. (16)

National Comprehensive Cancer Network (NCCN) Guidelines

The 2011 NCCN guidelines (v2.2012) recommend allogeneic bone marrow transplant as an alternative treatment option only for high-risk settings (Available online at: http://www.nccn.org/professionals/physician_gls/pdf/cml.pdf):

- patients who do not achieve hematologic remission after 3 months of imatinib therapy
- patients with no cytogenetic response or those in cytogenetic relapse at 6, 12, or 18 months, after achieving initial hematologic remission after 3 months of imatinib therapy
- patients progressing on a TKI to accelerated phase or blast crisis.

Autologous bone marrow transplant for CML is not addressed in the NCCN guidelines.

National Cancer Institute (NCI) Clinical Trial Database (PDQ®)

A search of the National Cancer Institute clinical trial database (PDQ®) identified 11 active Phase II/III trials in the U.S. including allografting, using various conditioning regimens, as well as different stem-cell sources and mobilization protocols. (Available online at: http://www.cancer.gov/search/ResultsClinicalTrials.aspx?protocolsearchid=7038344).

Government Regulations

National:

National Coverage Determination (NCD) for Stem Cell Transplantation (110.8.1), Effective Date of this Version 8/4/2010, Implementation date: 11/10/2010, Retrieved from: http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=45&ncdver=5&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=Michigan&CptHcpcsCode=38242&bc=gAAAABAAAAAA&, Accessed 7/23/12.

Indications and Limitations of Coverage

1. **Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)**

   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.

   a. Nationally Covered Indications

      The following uses of allogeneic HSCT are covered under Medicare:

      i. 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,

      ii. Effective for services performed on or after June 3, 1985, for the treatment of severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome.

      iii. Effective for services performed on or after August 4, 2010, for the treatment of Myelodysplastic Syndromes (MDS) pursuant to Coverage with Evidence Development (CED) in the context of a Medicare-approved, prospective clinical study.

2. **Autologous Stem Cell Transplantation (AuSCT)**

   Autologous stem cell transplantation (AuSCT) is a technique for restoring stem cells using the patient's own previously stored cells.

   a. Nationally Covered Indications

i. Effective for services performed on or after April 28, 1989, AuSCT is considered reasonable and necessary under §l862(a)(1)(A) of the Social Security Act (the Act) for the following conditions and is covered under Medicare for patients with:
   - Acute leukemia in remission who have a high probability of relapse and who have no human leucocyte antigens (HLA)-matched;
   - Resistant non-Hodgkin's lymphomas or those presenting with poor prognostic features following an initial response;
   - Recurrent or refractory neuroblastoma; or
   - Advanced Hodgkin's disease who have failed conventional therapy and have no HLA-matched donor.

ii. Effective October 1, 2000, single AuSCT is only covered for Durie-Salmon Stage II or III
patients that fit the following requirements:
   - Newly diagnosed or responsive multiple myeloma. This includes those patients with previously untreated disease, those with at least a partial response to prior chemotherapy (defined as a 50% decrease either in measurable paraprotein [serum and/or urine] or in bone marrow infiltration, sustained for at least 1 month), and those in responsive relapse; and,
   - Adequate cardiac, renal, pulmonary, and hepatic function.

iii. Effective for services performed on or after March 15, 2005, when recognized clinical risk factors are employed to select patients for transplantation, high dose melphalan (HDM) together with AuSCT is reasonable and necessary for Medicare beneficiaries of any age group with primary amyloid light chain (AL) amyloidosis who meet the following criteria:
   - Amyloid deposition in 2 or fewer organs; and,
   - Cardiac left ventricular ejection fraction (EF) greater than 45%.

Nationally Non-Covered Indications
Insufficient data exist to establish definite conclusions regarding the efficacy of AuSCT for the following conditions:
- Acute leukemia not in remission;
- Chronic granulocytic leukemia;
- Solid tumors (other than neuroblastoma);
- Up to October 1, 2000, multiple myeloma;
- Tandem transplantation (multiple rounds of AuSCT) for patients with multiple myeloma;
- Effective October 1, 2000, non primary AL amyloidosis; and,
- Effective October 1, 2000, thru March 14, 2005, primary AL amyloidosis for Medicare beneficiaries age 64 or older.

In these cases, AuSCT is not considered reasonable and necessary within the meaning of §l862(a)(1)(A) of the Act and is not covered under Medicare.

B. Other
All other indications for stem cell transplantation not otherwise noted above as covered or non-covered nationally remain at local contractor discretion.

Local:
There is no local coverage determination on this topic.

Michigan Department of Community Health:

Medicaid Provider Manual, Version Date: April 1, 2012, Retrieved from http://www.mdch.state.mi.us/dch-medicaid/manuals/MedicaidProviderManual.pdf, Accessed: 7/23/12.

6.6 Transplants

Heart, bone marrow, liver, lung, simultaneous pancreas/kidney and pancreas transplants are reimbursed at the hospital's Medicaid cost to charge ratio.

- Organ acquisition costs are reimbursed at 100% of charges when billed using either revenue code 0811 or 0812. This applies to heart, kidney, liver, lung, simultaneous pancreas/kidney, or pancreas transplants. **This does not apply to bone marrow transplants. All bone marrow transplant charges are reimbursed at the hospital's cost to charge ratio.**
- The letter of authorization for the transplant from the Office of Medical Affairs (OMA) or MHP must be attached to all transplant claims, otherwise, payment is denied.
- Indicate "PA letter submitted" in the Remarks Section of the submitted claim.
- For other transplant services not described by a specific DRG, identify in the Remarks Section the type of transplant that has been performed (i.e., small bowel transplant).
- If the donor and beneficiary are both Medicaid eligible, the services must be billed under each beneficiary's respective ID Number. If only the beneficiary is Medicaid eligible, bill services for both donor and beneficiary under the Medicaid beneficiary's ID Number.

All other insurance resources must be exhausted before Medicaid is billed. If Medicare eligibility is denied, the denial notice must be submitted with the claim.

(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 – Allogenic Hematopoietic Stem Cell Transplantation for Genetic Diseases and Acquired Anemias
- BMT – Autologous, for Malignant Astrocytomas and Gliomas
- BMT – Hematopoietic Stem Cell Transplant for Breast Cancer
- BMT – Hematopoietic Stem Cell Transplant for Treatment of Multiple Myeloma
- BMT – Hematopoietic Stem Cell Transplantation for Acute Lymphoblastic Leukemia
- BMT – Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia
- BMT – Hematopoietic Stem Cell Transplantation for Autoimmune Diseases
- BMT – Hematopoietic Stem Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma - Autologous or Allogeneic
- BMT – Hematopoietic Stem Cell Transplantation for CNS Embryonal Tumors and Ependymoma
- BMT – Hematopoietic Stem Cell Transplantation for Epithelial Ovarian Cancer
- BMT – Hematopoietic Stem Cell Transplantation for Hodgkin Lymphoma
- BMT – Hematopoietic Stem Cell Transplantation for Miscellaneous Solid Tumors in Adults
- BMT – Hematopoietic Stem Cell Transplantation for Non-Hodgkin Lymphomas
- BMT – Hematopoietic Stem Cell Transplantation for Primary Amyloidosis

- BMT – Hematopoietic Stem Cell Transplantation for Solid Tumors of Childhood
- BMT – Hematopoietic Stem Cell Transplantation for Waldenström's Macroglobulinemia
- BMT – Hematopoietic Stem Cell Transplantation in the Treatment of Germ-Cell Tumors
- Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Stem-Cell Transplant

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References

1. Maziarz RT. Who with chronic myelogenous leukemia to transplant in the era of tyrosine kinase inhibitors? Curr Opin Hematol 2008; 15(2):127-33.
2. Bhatia R, Verfaillie CM, Miller JS et al. Autologous transplantation therapy for chronic myelogenous leukemia. Blood 1997; 89(8):2623-34.
3. McGlave PB, Shu XO, Wen W et al. Unrelated donor marrow transplantation for chronic myelogenous leukemia: 9 years' experience of the national marrow donor program. Blood 2000; 95(7):2219-25.
4. Weisdorf DJ, Anasetti C, Antin JH et al. Allogeneic bone marrow transplantation for chronic myelogenous leukemia: comparative analysis of unrelated versus matched sibling donor transplantation. Blood 2002; 99(6):1971-7.
5. Giralt SA, Arora M, Goldman JM et al. Impact of imatinib therapy on the use of allogeneic haematopoietic progenitor cell transplantation for the treatment of chronic myeloid leukaemia. Br J Haematol 2007; 137(5):461-7.
6. Apperley JF. Managing the patient with chronic myeloid leukemia through and after allogeneic stem cell transplantation. Hematology Am Soc Hematol Educ Program 2006:226-32.
7. 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 2006; 355(23):2408-17.
8. Fernandez HF, Kharfan-Dabaja MA. Tyrosine kinase inhibitors and allogeneic hematopoietic cell transplantation for chronic myeloid leukemia: targeting both therapeutic modalities. Cancer Control 2009; 16(2):153-7.
9. Chakrabarti S, Buyck HC. Reduced-intensity transplantation in the treatment of haematological malignancies: current status and future-prospects. Curr Stem Cell Res Ther 2007; 2(2):163-88.
10. 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 2005; 106(9):2969-76.
11. Kantarjian H, Shah NP, Hochhaus A et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2010; 362(24):2260-70.
12. Saglio G, Kim DW, Issaragrisil S et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med 2010; 362(24):2251-9.
13. Baccarani M, Cortes J, Pane F et al. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol 2009; 27(35):6041-51.
14. von Bubnoff N, Duyster J. Chronic myelogenous leukemia: treatment and monitoring. Dtsch Arztebl Int 2010; 107(7):114-21.
15. Cervantes F, Mauro M. Practical management of patients with chronic myeloid leukemia. Cancer 2011; 117(19):4343-54.

16. Jain N, van Besien K. Chronic myelogenous leukemia: role of stem cell transplant in the imatinib era. Hematol Oncol Clin North Am 2011; 25(5):1025-48.
17. Pavlu J, Szydlo RM, Goldman JM et al. Three decades of transplantation for chronic myeloid leukemia: what have we learned? Blood 2011; 117(3):755-63.
18. Szatrowski TP. Progenitor cell transplantation for chronic myelogenous leukemia. Semin Oncol 1999; 26(1):62-6.
19. McGlave PB, De Fabritiis P, Deisseroth A et al. Autologous transplants for chronic myelogenous leukaemia: results from eight transplant groups. Lancet 1994; 343(8911):1486-8.
20. 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 2001; 86(6):596-601.
21. 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 2000; 28(2):210-5.
22. 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 1999; 24(3):259-64.
23. 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 2000; 26(11):1165-72.
24. 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 2000; 14(12):2064-9.
25. Pigneux A, Faberes C, Boiron JM et al. Autologous stem cell transplantation in chronic myeloid leukemia: a single center experience. Bone Marrow Transplant 1999; 24(3):265-70.
26. Mauro MJ, Deininger MW. Chronic myeloid leukemia in 2006: a perspective. Haematologica 2006; 91(2):152.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through July 23, 2012, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/13	10/16/12	10/16/12	This topic was formerly addressed in the following JUMP policies: • Allogeneic (Allogenic) Bone Marrow/Stem Cell Umbilical Cord Blood Transplants Donor Lymphocyte Infusion (Established) • Autologous Bone Marrow or Stem Cell Transplants (Investigational) • Policy formatted to mirror BCBSA. • Added “relative contraindications” to inclusionary/exclusionary section.

Next Review Date: 4th Qtr, 2013

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: BMT - HEMATOPOIETIC STEM-CELL TRANSPLANTATION FOR CHRONIC MYELOGENOUS LEUKEMIA

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	Refer to Medicare section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.
Blue Cross Complete of Michigan	Refer to Medicare section

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- 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.