Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 11/1/24**
(See policy history boxes for previous effective dates)

Title: BMT - Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia

Description/Background

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 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 100,000 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 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.(2)

For CML, 2 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. 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. 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 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 (HLAs) using cellular, serologic, or molecular techniques. HLA refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome six. 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 initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self-immunologic effector cells. While the slower GVM effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit medically tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by the cytotoxic drugs. Subsequent to graft

infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential 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 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 GVHD.

Reduced-Intensity Conditioning for Allo-HCT
Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses of cytotoxic drugs or 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. RIC 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.

Regulatory Status:

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

Medical Policy Statement

The safety and effectiveness of ***allogeneic*** hematopoietic cell transplantation using either a myeloablative conditioning regimen or a reduced-intensity conditioning (RIC) regimen for chronic myeloid leukemia have been established. It may be considered a useful therapeutic option in specified situations.

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

Inclusionary and Exclusionary Guidelines

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for RIC allogeneic HCT. These include those patients whose age (typically older than 60 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen.

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

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

Exclusions:

- *Autologous* hematopoietic cell transplantation as a treatment of chronic myeloid 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	38207	38208	38209	38210
38211	38212	38213	38214	38215	38230
38240	38242	38243	81265	81266	81267
81268	81370	81371	81372	81373	81374
81375	81376	81377	81378	81379	81380
81381	81382	81383	86812	86813	86816
86817	86821	S2150			

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

38206	38232	38241	S2140	S2142

Note: Code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Potential contraindications for transplant:

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

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

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

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

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, two domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice. The following is a summary of the key literature to date.

ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

Clinical Context and Test Purpose

The purpose of allogenic hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with chronic myeloid leukemia (CML).

The following PICOs were used to select literature to inform this review.

Populations

The relevant population of interest are individuals with CML.

Interventions

The therapy being considered is allogeneic hematopoietic cell transplantation.

Comparators

Comparators of interest include cytotoxic chemotherapy and treatment with tyrosine kinase inhibitors.

Outcomes

The general outcomes of interest are overall survival, disease specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up over months to years is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Randomized Controlled Trials

In the pre-tyrosine kinase inhibitor (TKI) era, allogeneic hematopoietic cell transplantation (allo-HCT) was the standard of care treatment for chronic myeloid leukemia (CML). Evidence in support of allo-HCT includes a randomized controlled trial (RCT) comparing primary HCT from a matched family donor (n=166) with best available drug treatment (n=261), which enrolled patients from 1997 to 2004.(3) There were no differences in overall survival (OS) between groups (10-year survival, 0.76 for HCT patients vs 0.69 for drug treatment patients). Those with low transplant risk treated with HCT had improved survival compared with those treated to medical therapy, but, after patients entered blast crisis, survival did not differ between groups.

The advent of TKI therapy has altered the treatment paradigm for CML such that most patients are treated initially with a TKI until disease progresses. While progression may occur within months of starting a TKI, progression may be delayed for years, as shown by the results of the IRIS trial (4) and other studies.(5,6) With the addition of three other TKIs (nilotinib, dasatinib, bosutinib) 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 allo-HCT is considered an option.(4,7,8)

Nonrandomized Studies

Several nonrandomized studies have compared treatment with TKI therapy and allo-HCT in CML patients. Liu et al (2013) evaluated outcomes for CML patients who underwent HCT after imatinib failure.(9) The authors retrospectively evaluated 105 patients with newly diagnosed chronic phase CML seen at a single institution from 1999 to 2011. Sixty-six patients received first-line imatinib therapy, 26 (treated before 2003) received interferon followed by imatinib, and 13 received front-line allo-HCT with curative intent. Twenty-two (21%) patients received allo-HCT overall, including 13 as front-line therapy and 9 following imatinib failure. Compared with those who received front-line allo-HCT, those who underwent HCT following imatinib failure had higher European Group for Blood and Marrow Transplantation (EBMT) risk score (p=0.03). Among those receiving allo-HCT (n=22; median follow-up, 134 months; range, 6-167 months), patients with imatinib failure and disease progression had a significantly worse OS (p=0.015) compared with those receiving allo-HCT as front-line therapy. Patients receiving front-line allo-HCT had a three-year OS rate of 91.7% (95% confidence interval [CI], 29 to 38 months); 1 patient in this group died of relapse and 1 of chronic graft-versus-host disease.

Xu et al (2015) retrospectively compared second-generation TKI therapy to allo-HCT in 93 patients in accelerated phase CML.(10) The second-generation TKI therapy group included 33 subjects, most of whom had been previously treated with another TKI (31 with imatinib, 2 with nilotinib). Of 60 patients treated with allo-HCT, 10 were treated with HCT for the first time and 50 had been previously treated with imatinib. Median OS was significantly shorter with second-generation TKI treatment than with allo-HCT (82 months). Median progression-free and event-free survival rates were similarly shorter with second-generation TKI treatment than with allo-HCT.

Zhang et al (2016) retrospectively compared imatinib (n=292) and allo-HCT (n=141) in patients with CML.(11) Survival rates were significantly longer in the imatinib group than in the allo-HCT group: 5-year EFS rates were 84% and 75% ($p<0.05$) and 5-year OS rates were 92% and 79%, both respectively. Findings were similar for patients with chronic and advanced phase disease.

Several studies have compared outcomes for CML patients treated with allo-HCT the pre- and post-TKI eras. While these studies generally report no worsening in treatment outcomes for allo-HCT following TKI, they are limited by the underlying differences in treatment regimens from different eras. In a retrospective analysis by Shen et al (2015) of 106 patients who underwent allo-HCT and who either did (n=36) or did not (n=70) receive prior treatment with TKIs, no significant differences were reported in 10-year relapse-free survival or OS rates.(12) However, TKI-treated patients had a higher incidence of 0.5-year transplant-related mortality. In another retrospective analysis comparing patients treated with allo-HCT in the pre-TKI era (1989-2001; n=39) with those treated in the TKI era (2002-2013; n=30), Chamseddine et al

(2015) reported longer three-year OS and leukemia-free survival among patients treated in the TKI era.(13)

Case Series

A number of case series, primarily involving single center, have reported outcomes for patients treated with allo-HCT following TKI treatment failure. In a 2015 series of 51 patients given allo-HCT, 32 of whom were treated for TKI resistance or intolerance, 8-year OS and event-free survival were 68% and 46%, respectively.(14) Another 2015 prospective series of 28 patients who underwent allo-HCT after failure of at least 2 TKIs reported deep molecular remission in 18 subjects.(15) However, all six patients transplanted in blast crisis died. In a smaller series, Zhao et al reported (2014) reported outcomes for 12 patients with CML with disease progression on imatinib who were treated with either dasatinib or nilotinib followed by allo-HCT at a single center.(16) After a median follow-up of 28 months (range, 12-37 months) after allo-HCT, 8 (66.7%) of 12 patients were alive, including seven with complete molecular remission.

In addition to being used prior to allo-HCT, TKI therapy may be used after HCT to prevent or treat disease relapse. Egan et al (2015) retrospectively analyzed patients at a single institution who underwent allo-HCT for CML and Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL) and had detectable BCR-ABL transcripts by polymerase chain reaction (PCR), as well as RNA available for sequencing of the ABL kinase domain, in both the pre- and post-HCT settings to evaluate the impact of pre-HCT variants in the ABL kinase domain on post-HCT relapse.(17) Among 95 patients with CML with available PCR transcripts, 10 (10.5%) were found to have pre-HCT ABL kinase variants known to confer resistance to TKIs. Of those with CML, 88.4% underwent myeloablative chemotherapy and 11.6% underwent nonmyeloablative chemotherapy. Twenty-nine CML patients received post-HCT TKIs: 19 (65.5%) for prophylaxis and 10 (34.5%) for treatment of refractory or relapsed disease. In 9 (64.2%) of the 14 patients with pre-HCT variants (which included both CML and Philadelphia chromosome–positive ALL), the same variants conferring TKI resistance were also detectable after allo-HCT. Among the 14 with pre-HCT variants, 8 (57.1%) received a TKI in the post-HCT setting and 7 (50%) demonstrated post-HCT refractory disease or relapse. Of the 7 with relapsed disease, 6 had been given a predictably ineffective TKI within the first 100 days after allo-HCT, based on variant analysis conducted by the authors.

Allo-HCT With Nonmyeloablative Conditioning

Techniques for allo-HCT have continued to develop, with important advancements in the use of nonmyeloablative or reduced-intensity conditioning (RIC) preparative regimens. Overall, among 9 studies compiled in a 2007 review, outcomes achieved with RIC allogeneic transplants have been similar to those with conventional allotransplants, with OS rates ranging from 35% at 2.5 years to 85% at 5 years among patients in chronic phase at transplant.(18) Among the studies assessed in this review, treatment-related mortality or non-relapse mortality ranged from 0% to 29% at 1 year. In the largest retrospective study, the European Group for Blood and Marrow Transplantation (2005) evaluated 186 patients.(19) The OS rate was 54% at 3 years using a variety of RIC regimens in patients in chronic phase I (n=118), chronic phase II (n=26), acute phase (n=30), and blast crisis (n=12). Among patients transplanted in the first chronic phase, the OS rate was 69% at 3 years.

RIC regimens have many of the same limitations as standard-intensity conditioning: relapse, 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 allo-HCT. Comparison of study results is further compromised by heterogeneity across patients, treatments, and outcome measures. Nonetheless, clinical evidence has suggested outcomes in CML are similar with myeloablative and RIC allo-HCT.(5,18,19)

Section Summary: Allogeneic Hematopoietic Cell Transplantation
Allo-HCT is accepted as a standard treatment in CML, although the use of targeted TKI therapy has allowed many patients who would have required allo-HCT to forestall or avoid transplantation altogether. Direct comparisons between myeloablative and nonmyeloablative conditioning (RIC) regimens are not available, but the available evidence has suggested that allo-HCT following nonmyeloablative conditioning regimens can lead to short- and medium-term survival rates that are on the order of those seen after myeloablative conditioning (MAC) regimens. Although research into the optimal timing of allo-HCT in the setting of TKI therapy is limited, the available evidence has suggested that pretreatment with TKIs does not worsen outcomes after allo-HCT and may improve outcomes.

AUTOLOGOUS HCT

Clinical Context and Test Purpose
The purpose of autologous hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with CML.

The following PICOs were used to select literature to inform this review.

Populations
The relevant population of interest are individuals with CML.

Interventions
The therapy being considered is autologous hematopoietic cell transplantation.

Comparators
Comparators of interest include cytotoxic chemotherapy and treatment with tyrosine kinase inhibitors.

Outcomes
The general outcomes of interest are overall survival, disease specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up over months to years is of interest for relevant outcomes.

Study Selection Criteria
Methodologically credible studies were selected using principles described above.

Review of Evidence

Nonrandomized Studies

A major limitation in the use of autologous HCT 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.(20) Even without such techniques, there are isolated case reports of partial cytogenetic remissions after autologous HCT, and a 1997 study suggested that patients undergoing such therapy may have improved survival compared with historical controls.(21)

In the pre-TKI era, there was active research into the use of autologous HCT or CML. McGlave et al (1994) reported outcomes of 200 consecutive autologous transplants using purged or unpurged marrow from 8 different transplant centers over seven years.(22) 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.(21)

Additional reports of small, uncontrolled studies with a total of 182 patients (range, 15-41 patients) given autologous HCT for CML included patient populations that varied across the studies. Some (2000, 2001) focused on newly diagnosed patients or those in the first year since diagnosis.(23,24) Others (1999, 2000) have focused on patients who did not respond to or relapsed after initial treatment using interferon alfa.(25,26) Finally, some focused on patients transplanted in the late chronic phase (2000) (27) or after transformation to accelerated phase or blast crisis (1999).(28) Although some patients achieved complete or partial molecular remission and long-term disease-free survival, these studies do not permit conclusions free from the influence of selection bias. All auto-transplanted patients included in these reports were treated before imatinib mesylate or newer TKIs became available.

Section Summary: Autologous HCT
No controlled studies have evaluated autologous HCT for treatment of CML. The available data consists of case reports and case series. In the largest series (N=200 patients), median survival was 36 months for patients transplanted during an accelerated phase and median survival data were not available for patients transplanted in chronic phase. Controlled studies are needed to permit conclusions about the impact of autologous HCT on health outcomes in patients with CML.

SUMMARY OF EVIDENCE

For individuals who have CML who receive allo-HCT, the evidence includes systematic reviews, randomized controlled trials, and multiple prospective and retrospective series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The introduction of 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 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 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. 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.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Society for Transplantation and Cellular Therapy

The guidelines by the American Society for Transplantation and Cellular Therapy (2020 – formerly the American Society for Blood and Marrow Transplantation) addressed indications for autologous and allogeneic HCT for CML.(30) 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 Guidelines

National Comprehensive Cancer Network (NCCN) chronic myeloid leukemia (CML) guidelines recommend allogeneic hematopoietic cell transplantation (allo-HCT) as an alternative treatment only for high-risk settings or in patients with advanced phase CML.(30) 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, 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.

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

Government Regulations
National:

Medicare National Coverage Determinations Manual, Chapter 1, Part 2, Section 110.23, "Stem Cell Transplantation." Effective date: 3/6/24; Implementation Date: 10/7/24
There are numerous autoimmune diseases and the Centers for Medicare and Medicaid Services have not issued a national coverage determination (NCD) for stem cell transplantation for each disease. CMS has a general NCD for stem cell transplantation which does not address chronic myeloid leukemia.

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

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

Related Policies

- BMT – Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia
- BMT – Hematopoietic Cell Transplantation for Acute Myeloid Leukemia and Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)
- BMT – Hematopoietic Cell Transplantation for Autoimmune Diseases
- BMT – Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Cell Lymphocytic Lymphoma – Autologous or Allogeneic
- BMT – Hematopoietic Cell Transplantation for CNS Embryonal Tumors and Ependymoma
- BMT – Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer

- BMT – Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias (Allogeneic)
- BMT – Hematopoietic Cell Transplantation for Germ-Cell Tumors
- BMT – Hematopoietic Cell Transplantation for Hodgkin Lymphoma
- BMT – Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
- BMT – Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms
- BMT – Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
- BMT – Hematopoietic Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome
- BMT – Hematopoietic Cell Transplantation for Primary Amyloidosis
- BMT – Hematopoietic Cell Transplantation for Solid Tumors of Childhood
- BMT – Hematopoietic Cell Transplantation for Waldenström's Macroglobulinemia
- BMT – Malignant Astrocytomas and Gliomas (Autologous)
- Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant
- Orthopedic Applications of Stem-Cell Therapy (Including Allografts and Bone Substitutes used with Autologous Bone Marrow)

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through May 24, 2024, 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.
5/1/14	2/24/14	3/3/14	Routine maintenance. No change in policy status.
7/1/15	4/24/15	5/8/15	Routine maintenance. Description, references and rationale updated.
7/1/16	4/19/16	4/19/16	Routine maintenance
1/1/17	10/11/16	10/11/16	Routine maintenance
1/1/18	10/19/17	10/19/17	Routine maintenance “Hematopoietic stem cell” changed to “hematopoietic cell” throughout policy; “myelogenous” changed to “myeloid” in policy title References and rationale updated
1/1/19	10/16/18	10/16/18	Routine maintenance Removed procedure codes 38220, 38221 and 86822
11/1/19	8/20/19		Routine maintenance
11/1/20	8/18/20		Routine maintenance
11/1/21	8/17/21		Routine maintenance
11/1/22	8/16/22		Routine maintenance
11/1/23	8/15/23		Routine maintenance (slp) Vendor Management: N/A
11/1/24	8/20/24		Routine maintenance (slp)

			Vendor Management: N/A

Next Review Date: 3rd Qtr. 2025

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

I. Coverage Determination:

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

II. Administrative Guidelines:

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