Kansas City

An Independent Licensee of the Blue Cross and Blue Shield Association

Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia

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Next Review: 7/2024

Blue KC has developed medical policies that serve as one of the sets of guidelines for coverage decisions. Benefit plans vary in coverage and some plans may not provide coverage for certain services discussed in the medical policies. Coverage decisions are subject to all terms and conditions of the applicable benefit plan, including specific exclusions and limitations, and to applicable state and/or federal law. Medical policy does not constitute plan authorization, nor is it an explanation of benefits.

When reviewing for a Medicare beneficiary, guidance from National Coverage Determinations (NCD) and Local Coverage Determinations (LCD) supersede the Medical Policies of Blue KC. Blue KC Medical Policies are used in the absence of guidance from an NCD or LCD.

NCDs
https://www.cms.gov/medicare-coverage-database/search-results.aspx?keyword=&keywordType=starts&areaId=s29&docType=NCD&contractOption=all

LCDs
https://www.cms.gov/medicare-coverage-database/search-results.aspx?keyword=&keywordType=starts&areaId=s29&docType=F,P&contractOption=all

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for high dose chemotherapy with hematopoietic cell support for chronic myeloid leukemia (CML) when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

Allogeneic hematopoietic cell transplantation (HCT) using a myeloablative conditioning regimen may be considered **medically necessary** as a treatment of chronic myeloid leukemia. As a treatment of CML when documentation is available

citing the reason Tyrosine Kinase Inhibitor (TKI) therapy is not appropriate as first line treatment.

Allogeneic HCT using a reduced-intensity conditioning regimen may be considered **medically necessary** as a treatment of chronic myeloid leukemia in individuals who meet clinical criteria for an allogeneic HCT but who are not considered candidates for a myeloablative conditioning allogeneic HCT.

When Policy Topic is not covered

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

Considerations

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

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

Description of Procedure or Service

Populations	Interventions	Comparators	Outcomes
Individuals: • With chronic myeloid leukemia	Interventions of interest are: • Allogeneic hematopoietic cell transplantation	Comparators of interest are: • Cytotoxic chemotherapy • Tyrosine kinase inhibitor(s)	Relevant outcomes include: • Overall survival • Disease-specific survival • Treatment-related mortality • Treatment-related morbidity
Individuals: • With chronic myeloid leukemia	Interventions of interest are: • Autologous hematopoietic cell transplantation	Comparators of interest are: • Cytotoxic chemotherapy • Tyrosine kinase inhibitor(s) • Allogeneic hematopoietic cell transplantation	Relevant outcomes include: • Overall survival • Disease-specific survival • Treatment-related mortality • Treatment-related morbidity

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. Chronic myeloid leukemia most often presents in a chronic phase from which it progresses to an accelerated and then a

blast phase. Allogeneic hematopoietic cell transplantation (allo-HCT) is a treatment option for CML.

Summary of Evidence

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

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

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 the fusion gene BCR-ABL, a tyrosine kinase that stimulates unregulated cell proliferation, inhibits cell apoptosis, creates genetic instability, and upsets interactions between CML cells and the bone marrow stroma only in malignant cells. The disease accounts for about 15% of newly diagnosed cases of leukemia in adults and occurs in 1 to 2 cases per 100,000 adults.[1,]

The natural history of the disease consists of an initial (indolent) chronic phase, lasting a median of 3 years, which typically transforms into an accelerated phase, followed by a "blast crisis," which is usually the terminal event. Most patients present in chronic phase, often with nonspecific symptoms secondary to anemia

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

Treatment

Historically, the only curative therapy for CML in blast phase has been allogeneic hematopoietic cell transplantation (allo-HCT), which was used more widely earlier in the disease process given the lack of other therapies for chronic phase CML. Drug therapies for chronic phase CML were limited to nonspecific agents including busulfan, hydroxyurea, and interferon-α.[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, 2 other tyrosine kinase inhibitors ([TKIs]; dasatinib, nilotinib) have received marketing approval from the U.S. Food and Drug Administration (FDA) as first-line therapies or following failure or patient intolerance of imatinib. Three additional TKIs (bosutinib, ponatinib, asciminib) have been approved for use in patients resistant or intolerant to prior therapy.

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

Hematopoietic Cell Transplantation

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

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

Conditioning for Hematopoietic Cell Transplantation

Conventional Conditioning

The conventional ("classical") practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of the initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease, which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of the bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the clinical definition of RIC is variable with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic

transplantation develops. Reduced-intensity conditioning regimens range from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. In this review, the term *reduced-intensity conditioning* will refer to all conditioning regimens intended to be nonmyeloablative.

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

Rationale

This evidence review was created in December 1999 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through November 15, 2022.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the 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 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 technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 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 (RCT) 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to

our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Allogeneic Hematopoietic Cell Transplantation

Clinical Context and Test Purpose

The purpose of allogeneic hematopoietic cell transplantation (allo-HCT) 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 question addressed in this evidence review is: Does the use of allo-HCT improve the net health outcomes of individuals with CML?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with CML.

Interventions

The therapy being considered is allo-HCT.

Comparators

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

Outcomes

The general outcomes of interest are overall survival (OS), disease-specific survival (DSS), 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 long-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-TKI era, allo-HCT was the standard of care for CML. Evidence in support of allo-HCT includes a 2015 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 10-year OS between groups (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 with medical therapy, but, after patients entered the 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 the 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 International Randomized Study of Interferon and STI571 trial[4,] and other studies.[5,6,] With the addition of 3 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 to 55 years) at which a myeloablative allo-HCT is considered an option.[4,7,8,]

Nonrandomized Studies

Several nonrandomized studies have compared treatment using TKI therapy with 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 first-line allo-HCT with curative intent. Twenty-two (21%) patients received allo-HCT overall, including 13 as first-line therapy and 9 following imatinib failure. Compared with those who received first-line allo-HCT, those who underwent HCT following imatinib failure had higher European Group for Blood and Marrow Transplantation risk scores (p=.03). Among those receiving allo-HCT (n=22; median follow-up, 134 months; range, 6 to 167 months), patients with imatinib failure and disease progression had a significantly worse OS (p=.015) compared with those receiving allo-HCT as first-line therapy. Patients receiving first-line allo-HCT had a 3-year OS rate of 91.7% (95% confidence interval, 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 with 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 (22 months) than with allo-HCT (82 months). Median progression-free survival 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) with allo-HCT (n=141) in patients who had CML.[11,] Survival rates were significantly longer in the imatinib group than in the allo-HCT group: 5-year event-free survival (EFS) rates were 84% and 75% ($p<.05$) 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 in the pre- and current TKI eras. While these studies have generally reported no worsening in treatment outcomes for allo-HCT following TKI therapy, they are limited by their underlying differences in treatment regimens from different eras. In a retrospective analysis by Shen et al (2015), of the 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 using allo-HCT in the pre-TKI era (1989 to 2001; n=39) with those treated in the TKI era (2002 to 2013; n=30), Chamseddine et al (2015) reported longer 3-year OS and leukemia-free survival among patients treated in the TKI era.[13,]

Case Series

A number of case series, primarily involving a 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 EFS rates were 68% and 46%, respectively.[14,] Another 2015 prospective series of 28 patients who underwent allo-HCT after the failure of at least 2 TKIs, reported deep molecular remission in 18 subjects.[15,] However, all 6 patients transplanted in blast crisis died. In a smaller series, Zhao et al (2014) reported on outcomes for 12 patients with CML who experienced disease progression on imatinib and received dasatinib or nilotinib followed by allo-HCT at a single-center.[16,]After a median follow-up of 28 months (range, 12 to 37 months) after allo-HCT, 8 (66.7%) of 12 patients were alive, including 7 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 and had detectable BCR-ABL transcripts by polymerase chain reaction, 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 polymerase chain reaction 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 (MAC),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 acute lymphoblastic leukemia), 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.

Allogeneic Hematopoietic Cell Transplantation 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 evaluated in a 2007 review, outcomes with RIC allogeneic transplants were 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 nonrelapse 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 1 (n=118), chronic phase 2 (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.

Reduced-intensity conditioning regimens have many of the same limitations as standard-intensity conditioning: relapse, graft-versus-host disease, 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 between myeloablative and RIC allo-HCT.[5,18,19,]

Section Summary: Allogeneic Hematopoietic Cell Transplantation

Allogeneic hematopoietic cell transplantation is accepted as a standard treatment in CML, although the use of targeted TKI therapy has allowed many patients who would previously have required allo-HCT to forestall or avoid transplantation altogether. Direct comparisons between myeloablative and nonmyeloablative 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 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 Hematopoietic Stem Cell Transplantation

Clinical Context and Test Purpose

The purpose of autologous HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with CML.

The question addressed in this evidence review is: Does the use of autologous HCT improve the net health outcomes of individuals with CML?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is patients with CML.

Interventions
The therapy being considered is autologous HCT.

Comparators
Comparators of interest include cytotoxic chemotherapy and treatment with TKIs.

Outcomes
The general outcomes of interest are OS, DSS, treatment-related mortality, and treatment-related morbidity.

Follow-up over months to years is of interest to relevant 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 long-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

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 for CML. McGlave et al (1994) reported on outcomes for 200 consecutive autologous

transplants using purged or unpurged marrow from 8 different transplant centers over 7 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, 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 a 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 to 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 have 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 autotransplanted patients included in these reports were treated before imatinib mesylate or newer TKIs became available.

Section Summary: Autologous Hematopoietic Stem Cell Transplantation
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.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network

National Comprehensive Cancer Network chronic myeloid leukemia (CML) guidelines (v.1.2023) recommend allogeneic hematopoietic cell transplantation (allo-HCT) as an alternative treatment only for high-risk settings or in patients with advanced phase CML.[29,] Relevant recommendations are:

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

Autologous HCT for CML is not addressed in these guidelines.

American Society for Transplantation and Cellular Therapy
In 2020, the guidelines by the American Society for Transplantation and Cellular Therapy (formerly the American Society for Blood and Marrow Transplantation) addressed indications for autologous and allo-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.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

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

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01760655	A Two Step Approach to Reduced Intensity Allogeneic Hematopoietic Stem Cell Transplantation for High Risk Hematologic Malignancies	72	Sept 2022
NCT03314974	Myeloablative Allogeneic Hematopoietic Cell Transplantation Using a Related or Unrelated Donor for the Treatment of Hematological Diseases	300	Nov 2025

NCT: national clinical trial.

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Billing Coding/Physician Documentation Information

38204 Management of recipient hematopoietic progenitor cell donor search and cell acquisition

38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogenic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
Q0083	Chemotherapy administration by other than infusion technique only (e.g., subcutaneous, intramuscular, push), per visit
Q0084	Chemotherapy administration by infusion technique only, per visit
Q0085	Chemotherapy administration by both infusion technique and other technique(s) (e.g.
S2140	Cord blood harvesting for transplantation
S2142	Cord blood-derived stem cell transplantation
S2150	Bone marrow or blood-derived peripheral stem cell harvesting and transplantation

ICD-10 Codes

C92.10-C92.12	Chronic myeloid leukemia, BCR/ABL-positive code range
C92.20-C92.22	Atypical chronic myeloid leukemia, BCR/ABL-negative code range

Additional Policy Key Words

Stem, SCT, Myelogenous, HSCT

Policy Implementation/Update Information

7/1/02	New policy added to the Medical section.
8/1/03	No policy statement changes. Changed from the Medical section to the Surgery and Transplant sections.
7/1/04	No policy statement changes.
7/1/05	No policy statement changes.
4/1/06	Considerations section revised to include general criteria.
7/1/06	No policy statement changes.
7/1/07	No policy statement changes.
7/1/08	No policy statement changes.
7/1/09	Policy statement updated to indicate reduced-intensity conditioning (RIC) allogeneic SCT as a treatment of chronic myelogenous leukemia in those who do not qualify for a myeloablative allogeneic SCT is investigational.
7/1/10	Policy statements revised to consider RIC allogeneic SCT as medically necessary in specific conditions.
7/1/11	No policy statement changes.
1/1/12	Coding updated.
7/1/12	No policy statement changes.
7/1/13	No policy statement changes.
7/1/14	Updated description on CPT 38240, 38241, 38242 and added CPT 38243. No policy statement changes.
7/1/15	No policy statement changes.
7/1/16	No policy statement changes.
7/1/17	In title and policy statements, "stem" removed and "myelogenous" changed to "myeloid".
7/1/18	No policy statement changes.
7/1/19	No policy statement changes.
7/1/20	No policy statement changes.
7/1/21	No policy statement changes.
7/1/22	No policy statement changes.
11/1/22	Updated first statement to include: "(CML). As a treatment of CML when documentation is available citing the reason Tyrosine Kinase Inhibitor (TKI) therapy is not appropriate as first line treatment. Updated "chronic myeloid leukemia" to CML.
7/1/23	No policy statement changes.
