Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia

Policy

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

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

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

Related Policies

- 7.01.50 Placental and Umbilical Cord Blood as a Source of Stem Cells
- 8.01.26 Hematopoietic Stem-Cell Transplantation for Acute Myeloid Leukemia
- 8.01.520 Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia

Policy Guidelines

Some patients for whom a conventional myeloablative allograft could be curative may be considered candidates for reduced-intensity conditioning allogeneic hematopoietic stem-cell transplantation (HCT). These include those patients whose age (typically >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.

For patients who qualify for a myeloablative allogeneic HCT on the basis of clinical status, either a myeloablative or reduced-intensity conditioning regimen may be considered medically necessary.
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### Description

Chronic myeloid leukemia (CML) is a hematopoietic stem cell disorder that is characterized by the presence of a chromosomal abnormality called the Philadelphia chromosome, which results from reciprocal translocation between the long arms of chromosomes 9 and 22. CML most often presents in a chronic phase from which it progresses to an accelerated and then a blast phase. Allogeneic hematopoietic cell transplantation (allo-HCT) is a treatment option for CML.

The evidence for allo-HCT for individuals who have CML includes systematic reviews, randomized controlled trials (RCTs), and multiple prospective and retrospective series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. Allo-HCT has been accepted as a standard treatment in CML. However, introduction of the tyrosine kinase inhibitors (TKIs) imatinib, dasatinib, nilotinib, bosutinib, and ponatinib has significantly changed the practice of HCT for CML. TKIs have replaced HCT as initial therapy in patients with chronic phase CML. However, a significant proportion of cases fails to respond to TKIs, develops resistance to them, or becomes unable to tolerate TKIs and goes on to allo-HCT. In addition, allo-HCT represents the only potentially curative option for those patients in the accelerated or blast phase. The currently available evidence suggests that TKI-pretreatment does not lead to worse outcomes if HCT is needed.

Myeloablative conditioning regimens prior to HCT are used in younger (<60 years) patients without significant comorbidities. However, for patients with more comorbidities and/or more advanced ages in whom myeloablative conditioning regimens would be prohibitively high risk, evidence suggests 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.

### Hematopoietic Stem-Cell Transplant

#### Overview

Hematopoietic cell transplantation (HCT) is a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs with or without whole body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are
antigenically “naive” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD). Cord blood is discussed in greater detail in another policy. (See Related Policies.)

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (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 (with the exception of umbilical cord blood).

**Conditioning for HCT**

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

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

**RIC for Allogeneic HCT**

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 nonrelapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For the purposes of this Policy, the term “reduced-intensity conditioning” will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

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

**Chronic Myeloid Leukemia**

**Overview**

CML is a hematopoietic stem-cell disorder that is characterized by the presence of a chromosomal abnormality...
called the Philadelphia chromosome, which results from reciprocal translocation between the long arms of chromosomes 9 and 22. This cytogenetic change results in constitutive activation of BCR-ABL, a tyrosine kinase (TK) that stimulates unregulated cell proliferation, inhibition of apoptosis, genetic instability, and perturbation of the interactions between CML cells and the bone marrow stroma only in malignant cells. CML accounts for about 15% of newly diagnosed cases of leukemia in adults and occurs in about 1 to 2 cases per 100,000 adults.\(^{(1)}\)

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

**Therapy for CML**

Historically, the only curative therapy for CML in blast phase was HCT, and HCT was used more widely earlier in the disease process given the lack of other therapies for chronic phase CML. Drug therapies for chronic phase CML were limited to nonspecific agents including busulfan, hydroxyurea, and interferon-alpha.\(^{(1)}\)

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 usually curative and is ineffective in 20% to 30%, initially or due to emergence 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 (FDA) as front-line therapies or following failure or patient intolerance of imatinib. Two additional TKIs (bosutinib, ponatinib) have been approved for use in patients resistant or intolerant to prior therapy.

For patients who progress on imatinib, the therapeutic options include increasing the imatinib dose, changing to another TKI, or allo-HCT. Detection of BCR-ABL mutations may be important in determining an alternative TKI; the presence of T315I mutation is associated with resistance to all TKIs except ponatinib and may indicate the need for allo-HCT or an experimental therapy. TKIs have been associated with long-term remissions; if progression occurs after exhausting TKI therapy, allo-HCT is generally indicated and offers the potential for cure.

**Scope**

Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

**Benefit Application**

The following considerations may supersede this policy:

- State mandates requiring coverage for autologous bone marrow transplantation offered as part of clinical trials of autologous bone marrow transplantation approved by the National Institutes of Health (NIH).
- Some plans may participate in voluntary programs offering coverage for patients participating in NIH-approved clinical trials of cancer chemotherapies, including autologous bone marrow transplantation.
Some contracts or certificates of coverage may include specific conditions in which autologous bone marrow transplantation would be considered eligible for coverage.

**Rationale**

This policy was originally created in December 1999 and has been updated regularly with searches of the MEDLINE database. The most recent literature review was performed through November 9, 2016. Following is the summary of the key literature to date.

**Allogeneic Hematopoietic Cell Transplantation**

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. 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).(3) 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 trial4 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 50-55 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.(10) They 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 3-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 (GVHD).

Xu et al (2015) retrospectively compared second-generation TKI therapy to allo-HCT in 93 patients with 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 (EFS) 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 phase 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 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 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 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 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 outcomes for 12 patients with CML with disease progression on imatinib who received 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 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 (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 was 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.

**HCT With Nonmyeloablative Conditioning**

Techniques for allogeneic 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 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. (18) Among the studies included in this review, treatment-related mortality or nonrelapse mortality (NRM) ranged from 0% to 29% at 1 year. In the largest experience, a retrospective European Group for Blood and Marrow Transplantation 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). (19) Among patients transplanted in the first chronic phase, 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 HCT. 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 HCT. (5,18,19)

**Section Summary**
Allo-HCT 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 conditioning (RIC) regimens are not available, but the available evidence suggests 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 regimens. Although research into the optimal timing of allo-HCT in the setting of TKI therapy is limited, the available evidence suggests that pretreatment with TKIs does not worsen outcomes after allo-HCT and may actually improve outcomes.

**Autologous HCT**

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 have been isolated case reports of partial cytogenetic remissions after autologous HCT, and one study (1997) has 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 (2004) reported outcomes of 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, 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 autotransplants 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) 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.(28) 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 selection bias. All autotransplanted patients included in these reports were treated before imatinib mesylate or newer TKIs became available.

**Section Summary**

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.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 1.

### Table 1. Summary of Key Trials

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Summary of Evidence

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

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

Practice Guidelines and Position Statements

National Comprehensive Cancer Network Guidelines

Current National Comprehensive Cancer Network (NCCN) guidelines (v.1.2017) recommend allogeneic hematopoietic cell transplantation (allo-HCT) as an alternative treatment only for high-risk settings or in patients with advanced-phase chronic myeloid leukemia (CML). Relevant recommendations are:

- The use of first-line treatment with allogeneic HCT for:
  - Patients presenting with blast phase at diagnosis
  - Patients with T315I and other BCR-ABL1 mutations that are resistant to all TKIs
  - Rare patients intolerant to all TKIs

- For chronic phase CML:
  - Allogeneic HCT is recommended for patients with T315I mutations that are resistant to all TKIs.
  - Evaluation for HCT is recommended if the response milestones are not achieved, as indicated by:
    - BCR-ABL1/ABL1 >10% or lack of partial cytogenetic response (PCyR) at 3 and 6 months.
    - “Less than PCyR or BCR-ABL1 transcripts >10% by QPCR (IS) at 12 months
    - Cytogenetic relapse at 12 or 18 months.

- For advanced-phase and blast-phase CML:
  - Allogeneic HCT should be considered for patients with AP-CML [advance phase CML] or BP-
CML [blast phase CML].”

NCCN guidelines state: “Nonmyeloablative allogeneic HCT [hematopoietic cell transplantation] is a well-tolerated treatment option for patients with a matched donor and the selection of patients is based on their age and the presence of comorbidities.”

Autologous HCT for CML is not addressed in the NCCN guidelines.

**American Society for Blood and Marrow Transplantation**

In 2015, guidelines by the American Society for Blood and Marrow Transplantation addressed indications for autologous and allogeneic HCT for CML. (30) Recommendations are listed in Table 2.

### Table 2. ASBMT Recommendations on Allogeneic and Autologous HCT for CML

<table>
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<td>Blast phase</td>
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</table>

ASBMT: American Society for Blood and Marrow Transplantation; C: Standard of care, clinical evidence available, CML: chronic myeloid leukemia; HCT: hematopoietic cell transplantation; N: Not generally recommended; S: standard of care; TKI: tyrosine kinase inhibitor.

**European LeukemiaNet Guidelines**

In 2013, European LeukemiaNet issued updated guidelines for the management of CML. (31) These guidelines recommend the use of allogeneic HCT in the following situations:

- For chronic phase treatment:
  - Consider HCT as second-line therapy after failure of nilotinib or dasatinib as first-line therapy.
  - Recommend HCT in all eligible patients as third-line therapy after failure of or intolerance to 2 TKIs.
  - Consider HCT at any point if T315I mutation.

- For accelerated or blast phase in newly-diagnosed, TKI-naïve patients:
  - Begin imatinib or dasatinib.
  - Recommend HCT for all blast phase patients and for accelerated phase patients who do not achieve an optimal response.

- For accelerated or blast phase as progression from chronic phase in TKI-pretreated patients: recommend HCT for all patients (after initiation of one of the TKIs that was not previously used or ponatinib in the case of T315I mutations).

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**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.

References


Appendix

N/A

History

<table>
<thead>
<tr>
<th>Date</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>02/01/00</td>
<td>Add to Therapy Section - New Policy — replaces 8.01.15, original master policy on high-dose chemotherapy for miscellaneous malignancies. However, policy statement is unchanged.</td>
</tr>
<tr>
<td>01/14/03</td>
<td>Replace Policy - Policy updated, new references added; no change in policy statement.</td>
</tr>
<tr>
<td>06/17/03</td>
<td>Replace Policy - Update CPT codes only.</td>
</tr>
<tr>
<td>08/12/03</td>
<td>Replace Policy - Reviewed and recommended for adoption without any changes by Company Oncology Advisory Panel July 22, 2003.</td>
</tr>
<tr>
<td>10/12/04</td>
<td>Replace Policy - Policy reviewed with literature search; no change in policy statement. Approved by OAP 10/29/04, returning to MPC.</td>
</tr>
<tr>
<td>01/10/06</td>
<td>Replace Policy - Policy reviewed with literature search; no change to policy statement.</td>
</tr>
<tr>
<td>06/02/06</td>
<td>Disclaimer and Scope updates - No other changes.</td>
</tr>
</tbody>
</table>
Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA).

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You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the OCR Portal, or by mail or phone at:

Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

If you need these services, contact the Civil Rights Coordinator.

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