# Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia

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**Precertification is required for this service.**

## I. Description

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

For individuals who have CML who receive allo-HCT, the evidence includes systematic reviews, randomized controlled trials (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.

## Background

### 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 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, 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.

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. 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 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.

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, 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 (OS) of patients who present in chronic phase is greater than 95% at 2 years and 80% to 90% at 5 years.

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 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 an 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**

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

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is critical for achieving a good outcome with allo-HCT. Compatibility is established by typing of human leukocyte antigens (HLAs) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

**Conventional Conditioning for HCT**

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

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal

hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed when the patient's disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

**Reduced-Intensity Conditioning for Allo-HCT**

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden and 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 allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For this evidence review, RIC will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

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

**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, title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

## II. Criteria

A. Allogeneic hematopoietic cell transplantation (HCT) using a myeloablative conditioning regimen is covered as a treatment of chronic myelogenous leukemia.

B. Allogeneic hematopoietic cell transplantation using a reduced-intensity conditioning regimen is covered as a treatment of chronic myelogenous leukemia in patients who meet clinical criteria for an allogeneic HCT but who are not considered candidates for a myeloablative conditioning allogeneic HCT.

## III. Guidelines

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

B. 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 covered.

## IV. Limitations/Exclusions

Autologous hematopoietic cell transplantation as a treatment of chronic myelogenous leukemia is not covered as it is not known to be effective in improving health outcomes.

## V. Administrative Guidelines

A. Precertification is required for a transplant evaluation and for the transplant itself and should be submitted by the proposed treating facility. To precertify, please complete HMSA's Precertification Request and mail or fax the form, or use iExchange as indicated along with the required documentation.

| CPT Codes | Description |
|---|---|
| 38204 | Management of recipient hematopoietic cell donor search and cell acquisition |
| 38205 | Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic |
| 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, per donor |
| 38209 | ;thawing of previously frozen harvest, with washing, per donor |
| 38210 | ;specific cell depletion with harvest, T-cell depletion |
| 38211 | ;tumor cell depletion |
| 38212 | ;red blood cell removal |
| 38213 | ;platelet depletion |
| 38214 | ;plasma (volume) depletion |

| | |
|---|---|
| 38215 | ;cell concentration in plasma, mononuclear, or buffy coat layer |
| 38230 | Bone marrow harvesting for transplantation; allogeneic |
| 38232 | ;autologous |
| 38240 | Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor |
| 38241 | ;autologous transplantation |
| **HCPCS Code** | **Description** |
| Q0083 -Q0085 | Chemotherapy, administer code administration |
| J9000 -J9999 | Chemotherapy drug code administration |
| S2140 | Cord blood harvesting for transplantation, allogeneic |
| S2142 | Cord blood-derived stem-cell transplantation, allogeneic |
| S2150 | Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic, and emergency services) |

| **ICD-10-CM** | **Description** |
|---|---|
| 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 |
| **ICD-10-PCS** | **Description** |
| 30233G0, 30233X0, 30233Y0 | Administration, circulatory, transfusion, peripheral vein, percutaneous, autologous, code by substance (bone marrow, cord blood or stem cells, hematopoietic) |
| 30233G2, 30233X2, 30233Y2 | Administration, circulatory, transfusion, peripheral vein, percutaneous, allogeneic related, code by substance (bone marrow, cord blood or stem cells, hematopoietic) code list |
| 30233G3, 30233X3, 30233Y3 | Administration, circulatory, transfusion, peripheral vein, percutaneous, allogeneic unrelated, code by substance (bone marrow, cord blood or stem cells, hematopoietic) code list |
| 30233G4, 30233X4, 30233Y4 | Administration, circulatory, transfusion, peripheral vein, percutaneous, allogeneic unspecified, code by substance (bone marrow, cord blood or stem cells, hematopoietic) code list |
| 30243G0, 30243X0, 30243Y0 | Administration, circulatory, transfusion, central vein, percutaneous, autologous, code by substance (bone marrow, cord blood or stem cells, |

| | |
|---|---|
| | hematopoietic) code list |
| 30243G2, 30243X2, 30243Y2 | Administration, circulatory, transfusion, central vein, percutaneous, allogeneic related, code by substance (bone marrow, cord blood or stem cells, hematopoietic) code list |
| 30243G3, 30243X3, 30243Y3 | Administration, circulatory, transfusion, central vein, percutaneous, allogeneic unrelated, code by substance (bone marrow, cord blood or stem cells, hematopoietic) code list |
| 30243G4, 30243X4, 30243Y4 | Administration, circulatory, transfusion, central vein, percutaneous, allogeneic unspecified, code by substance (bone marrow, cord blood or stem cells, hematopoietic) code list |
| 30250G0, 30250X0, 30250Y0 | Administration, circulatory, transfusion, peripheral artery, open, autologous, code by substance (bone marrow, cord blood or stem cells, hematopoietic) |
| 30250G1, 30250X1, 30250Y1 | Administration, circulatory, transfusion, peripheral artery, open, nonautologous, code by substance (bone marrow, cord blood or stem cells, hematopoietic) |
| 30253G0, 30253X0, 30253Y0 | Administration, circulatory, transfusion, peripheral artery, percutaneous, autologous, code by substance (bone marrow, cord blood or stem cells, hematopoietic) |
| 30253G1, 30253X1, 30253Y1 | Administration, circulatory, transfusion, peripheral artery, percutaneous, nonautologous, code by substance (bone marrow, cord blood or stem cells, hematopoietic) |
| 6A550ZT, 6A550ZV | Extracorporeal Therapies, pheresis, circulatory, single, code by substance (cord blood, or stem cells, hematopoietic) |
| 6A551ZT, 6A551ZV | Extracorporeal Therapies, pheresis, circulatory, multiple, code by substance (cord blood, or stem cells, hematopoietic) |

## VI. Scientific Background

This policy has been updated regularly with searches of the MEDLINE database. The most recent literature search was performed throughDecember 11, 2017. Following is the summary of the key literature to date.

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, 2 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**

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). 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. 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.

**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. 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. 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. 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. 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.

**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. 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. 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. 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. Among the studies included in this review, treatment-related mortality or nonrelapse mortality ranged from 0% to 29% at 1 year. In the largest experience, a 2005 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). 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.

**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 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 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 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 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. Even without such techniques, there have been isolated case reports of partial cytogenetic remissions after autologous HCT, and 1 study (1997) has suggested that patients undergoing such therapy may have improved survival compared with historical controls.

In the pre-TKI era, there was active research into the use of autologous HCT for CML. McGlave et al (1994) reported 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 small, single-institution case series using a variety of techniques to enrich the population of normal stem cells among the harvested cells.

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. Others (1999, 2000) have focused on patients who did not respond to or relapsed after initial treatment using interferon alfa. Finally, some focused on patients transplanted in the late chronic phase (2000) or after transformation to accelerated phase or blast crisis (1999). 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 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 chronic myeloid leukemia (CML) who receive allogeneic hematopoietic cell transplantation (allo-HCT), the evidence 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.

**Ongoing 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** | | | |
| NCT01366612 | PRO#1278: A Phase III Study of Fludarabine and Busulfan Versus Fludarabine, Busulfan and Low Dose Total Body Irradiation in Patients Receiving an Allogeneic Hematopoietic Stem Cell Transplant | 54 | Dec 2015 (ongoing) |
| NCT00739141 | Conditioning Regimen and the Transplantation of Unrelated Donor Umbilical Cord Blood in Patients with Hematologic Malignancies | 80 | Aug 2017 |
| NCT01231412 | A Randomized Phase III Study to Determine the Most Promising Postgrafting Immunosuppression for Prevention of Acute GVHD After Unrelated Donor Hematopoietic Cell Transplantation Using Nonmyeloablative Conditioning for Patients With Hematologic Malignancies: A Multi-center Trial | 300 | Sep 2017 |
| NCT02333838 | Reduced Toxicity Conditioning Prior to Unrelated Cord Cell Transplantation for High Risk Myeloid Malignancies (TBF-Cord) | 57 | Mar 2018 |
| NCT02638467 | Allogeneic Stem Cell Transplantation in Chronic Myeloid Leukemia Failing TKIs Therapy | 20 | Jun 2018 |
| NCT00036738 | Fludarabine Phosphate and Total-Body Irradiation Followed by Donor Peripheral Blood Stem Cell | 30 | Oct 2018 |

| | | | |
|---|---|---|---|
| | Transplant in Treating Patients with Acute Lymphoblastic Leukemia or Chronic Myelogenous Leukemia That Has Responded to Treatment with Imatinib Mesylate, Desatinib, or Nilotinib | | |
| NCT00709592 | Reduced Intensity Total Body Irradiation + Thymoglobulin Followed by Allogeneic PBSCT | 42 | Sep 2020 |

NCT: national clinical trial.

**Practice Guidelines and Position Statements**

National Comprehensive Cancer Network (NCCN) Guidelines

Current National Comprehensive Cancer Network (NCCN) guidelines (v.3.2018) 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:

- "Allogenic HCT is no longer recommended as a first-line treatment option for CP [chronic phase]-CML"
- "Allogenic HCT is an appropriate first-line treatment option for the very rare patients presenting with blast phase at diagnosis, patients with T315I and other BCR-ABL1 mutations that are resistant to all TKIs [tyrosine kinase inhibitors], and for the rare patients intolerant to all TKIs"
- Evaluation for allogeneic HCT…..it is recommended for all patients with AP [accelerated phase] CML or BP [blast phase] CML:

NCCN guidelines state: "Nonmyeloablative allogeneic HCT [hematopoietic cell transplantation] is a welltolerated 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 1.

**Table 1. ASBMT 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, TKI intolerant | C | N |
| Chronic phase, TKI refractory | C | N |
| Chronic phase 2+ | S | N |
| Accelerated phase | S | N |
| Blast phase | S | N |

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**

In 2013, European LeukemiaNet updated its guidelines on the management of CML.31 These guidelines recommended the use of allo-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, tyrosine-kinase inhibitor (TKI)□naive 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 1 of the TKIs that was not previously used or ponatinib in the case of T315I mutations).

**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** | | | |
| NCT02638467 | Allogeneic Stem Cell Transplantation in Chronic Myeloid Leukemia Failing TKIs Therapy | 20 | Jun 2018 |
| NCT00036738 | Fludarabine Phosphate and Total-Body Irradiation Followed by Donor Peripheral Blood Stem Cell Transplant in Treating Patients with Acute Lymphoblastic Leukemia or Chronic Myelogenous Leukemia That Has Responded to Treatment with Imatinib Mesylate, Desatinib, or Nilotinib | 30 | Oct 2018 |
| NCT00709592 | Reduced Intensity Total Body Irradiation + Thymoglobulin Followed by Allogeneic PBSCT | 42 | Sep 2020 |

NCT: national clinical trial.

## VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

## VIII. References


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