Hematopoietic Cell Transplantation for Chronic Myelogenous Leukemia

Effective: November 1, 2024

Next Review: August 2025
Last Review: September 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

I.   Allogeneic hemopoietic cell transplantation may be considered **medically necessary** as a treatment of chronic myelogenous leukemia using either of the following regimens (A. or B.):

    A.   Myeloablative conditioning regimen (see Policy Guidelines).

    B.   Reduced-intensity conditioning (RIC) regimen in patients who are not considered candidates for a myeloablative conditioning allogeneic hemopoietic cell transplantation (see Policy Guidelines).

II. Allogeneic hemopoietic cell transplantation is considered **not medically necessary** as a treatment of chronic myelogenous leukemia when Criterion I. is not met.

III. Autologous hematopoietic cell transplantation is considered **investigational** as a treatment of chronic myelogenous leukemia.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

REDUCED-INTENSITY CONDITIONING

Patients who meet criteria for allogeneic hemopoietic cell transplantation but whose advanced age (typically older than 60 years) and existing comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude the use of a standard myeloablative conditioning regiment, may be considered candidates for *reduced-intensity conditioning (RIC).*

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant
- If patient requires a reduced-intensity conditioning (RIC) regimen – documentation supporting reasons patient is unable to tolerate a standard myeloablative conditioning regimen

CROSS REFERENCES

1. Genetic Testing for Myeloid Neoplasms and Leukemia, Genetic Testing, Policy No. 59
2. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
3. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16
4. Allogeneic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms, Transplant, Policy No. 45.24

BACKGROUND

Chronic myelogenous leukemia (CML) is a hematopoietic 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.

HEMATOPOIETIC CELL TRANSPLANTATION

Broadly speaking, there are two types of hematopoietic cell transplants (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease (e.g. lymphoma) with myeloablative doses of chemotherapy (with or without radiation) that are active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells 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 cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous 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.

CONVENTIONAL PREPARATIVE 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 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 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 cells obtained from the patient prior to 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 prior to engraftment, but not GVHD.

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HCT

Reduced-intensity conditioning (RIC) refers to the conditioning with 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 not only to reduce disease burden, but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic 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 non-myeloablative, as opposed to fully myeloablative (conventional) regimens.

CHRONIC MYELOGENOUS LEUKEMIA

Chronic myelogenous leukemia (CML) is a hematopoietic 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 approximately 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 three years, which typically transforms into an accelerated phase, followed by a "blast crisis," which is usually the terminal event. Most patients present in chronic phase, often with nonspecific symptoms 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 four to six years. However, successive remissions are invariably shorter and more difficult to achieve than their predecessors.

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 curative and is ineffective in 20% to 30%, initially or due to development of BCR-ABL mutations that cause resistance to the drug. The overall survival (OS) of patients who present in chronic phase is greater than 95% at two years and 80% to 90% at five years.[2] Two other TK inhibitors (TKIs; dasatinib, nilotinib) have received marketing approval from the U.S. Food and Drug Administration (FDA) to treat CML following failure or patient intolerance of imatinib. In any case, allogeneic HCT remains the only treatment capable of inducing durable remissions or cure in CML patients.

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 the T315I mutation is associated with resistance to all TKIs and should indicate the need for allo-HCT or an experimental therapy. In any case, allogeneic HCT remains the only treatment capable of inducing durable remissions or cure in CML patients. TKIs have been associated with long-term remissions; however, if progression occurs on TKI therapy, allo-HCT is generally indicated and offers the potential for cure.

EVIDENCE SUMMARY

The principal outcomes associated with treatment of hematologic malignancies are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Risk of graft-versus-host disease is another primary outcome among patients undergoing allogeneic hematopoietic cell transplantation (HCT). Ideally, in order to understand the impact of HCT for treatment of chronic myelogenous leukemia, comparative clinical trials that compare this therapy to standard medical treatment, such as treatment with a TKI, or among patients not able to tolerate TKIs, or for whom TKIs fail, standard conditioning regimens, are needed. Further, for treatment of hematologic cancers, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits associated with treatment to understand the net treatment effect.

ALLOGENEIC HCT

Allogeneic hematopoietic cell transplantation (HCT) is the only known potentially curative therapy for chronic myelogenous leukemia (CML) and has been accepted as a standard treatment. It became a standard of treatment for CML in the 1980's when the graft-versus-leukemia (GVL) effect was shown to be the critical factor for long-term disease control.[3] Studies in patients with chronic phase disease who received an HLA-matched sibling donor transplant had a 45% to 75% probability of long-term disease-free survival, while those transplanted with more advanced disease had a 15% to 40% long-term survival.[4] Young, good-risk patients who received transplants early in the chronic phase from HLA-matched but unrelated donors had a 40% to 60% chance of long-term survival, which was lower than that of similar patients transplanted from matched sibling donors.[5, 6]

Allogeneic HCT was once commonly performed for the treatment of CML, but with the advent of TKIs, this has changed. A retrospective analysis of data from the Center for International Blood and Marrow Transplant Research Center (CIBMTR) showed that transplantation for CML was in decline prior to U.S. Food and Drug Administration (FDA) approval of imatinib in 2001.[7] Subsequently, long-term follow-up results from the International Randomized Study of Interferon and STI 571 (IRIS) of imatinib mesylate, plus the availability of two additional approved TKI agents (nilotinib and dasatinib), have caused modification of the timing of application of allogeneic cell transplant.[8-10] This procedure now is typically delayed in patients with newly diagnosed CML, who will receive imatinib mesylate as front-line treatment. It also may only be used early when a complete molecular response to the drug fails or is not achieved soon after starting imatinib administration. The currently-available evidence suggests that TKI-pretreatment does not lead to worse outcomes if HCT is needed. Techniques for

allogeneic HCT have continued to develop, with important advancements in the use of nonmyeloablative or reduced-intensity conditioning (RIC) preparative regimens.

Systematic Review

A 2012 comparative effectiveness review published by the Agency for Healthcare Research and Quality (AHRQ) on the use of HCT in the pediatric population considered allogenic HCT for the treatment of CML.[11] The review cited the risk of disease relapse with interruption in TKI therapy, which complicates the decision to proceed to allogeneic HCT. The review concluded that there is no evidence to inform the "decision and timing to proceed to allogeneic HCT" following treatment with TKI therapy.

Randomized Controlled Trials

In a prospective, 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 between groups (10-year survival 0.76 for HCT patients vs 0.69 for best available drug treatment patients).[12] Those with low transplant risk treated with HCT had improved survival compared with those treated with medical therapy, but after patients entered blast crisis, survival did not differ between groups.

Nonrandomized Studies

Wu (2019) reported on late mortality in patients with CML who underwent blood or bone marrow transplant either with or without prior TKI therapy.[13] The authors analyzed data from the Blood or Marrow Transplant Survivor Study. General population age-specific, sex-specific, and calendar-specific mortality rates from 447 patients with CML who underwent transplant were used to calculate standardized mortality ratios (SMRs). SMRs for patients with and without pre-transplant TKI were 6.4 and 6.4, respectively (p=0.8) for all patients and 11.6 and 8.1, respectively, for those with high-risk disease (p=0.2). For all patients, the 20-year cumulative incidence of CML-related and non-CML-related mortality, which were comparable between those with and without pre-transplant TKI, were 6% and 36%, respectively.

Radujkovic (2019) evaluated outcomes in patients treated with allo-HCT for blast crisis CML.[14] This retrospective registry-based study included 170 patients in the analysis, of which 95 were in remission and 75 had active blast crisis. A multivariate analysis indicated that active blast crisis at transplant was the strongest factor associated with decreased OS (HR 1.87; p=0.010) and shorter leukemia-free survival (HR 1.69; p=0.017). Risk factors for inferior survival in patients with blast crisis in remission at transplant included age ≥45 years, performance status ≤80%, >12 months between diagnosis of blast crisis to transplant, myeloablative conditioning and unrelated donor transplant. The only factor significantly associated with longer leukemia-free survival in patients with active blast crisis was unrelated donor transplant.

Chhabra (2018) performed a retrospective analysis of data from the Center for International Blood and Marrow Transplant Research database to compare RIC and myeloablative conditioning.[15] The analysis included 1,395 patients that received RIC (n=191) or MAC (n=1,204) allo-HCT for CML. Patients in blast phase at transplant and alternative donor transplants were excluded from the analysis. There was no statistically significant difference between groups for the primary outcome, OS. Leukemia-free survival and nonrelapse mortality also did not differ significantly between groups. However, there were statistically significant differences in cumulative incidence of chronic graft-versus-host disease (lower with RIC,

hazard ratio (HR), 0.77; p=0.02) and risk of early relapse after allo-HCT (higher with RIC, HR 1.85; p=0.001).

Zhang (2016) retrospectively compared imatinib (n=292) and allo-HCT (n=141) in patients with CML.[16] Survival rates were significantly longer in the imatinib group than in the allo-HCT group: five-year EFS rates were 84% and 75% (p<0.05) and five-year OS rates were 92% and 79%, both respectively. Findings were similar for patients with chronic phase and advanced phase disease.

Overall, among nine studies compiled in a non-systematic review by Chakrabarti (2007), 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 five years among patients in chronic phase 1 at transplant.[17] Among the studies included in this review, treatment-related mortality or nonrelapse mortality (NRM) ranged from 0% at one year to 29% at one year. In the largest experience, a retrospective European Group for Blood and Marrow Transplantation (EMBT) study of 186 patients, overall survival (OS) was 54% at three 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).[18] Among patients transplanted in the first chronic phase (CP1), OS was 69% at three years.

Xu (2015) retrospectively compared second-generation TKI therapy with allo-HCT in 93 patients with accelerated-phase CML.[19] The second-generation TKI therapy group included 33 subjects, most of whom had been previously treated with another TKI (n=31 with imatinib and n=2 with nilotinib). Of 60 patients treated with allo-HCT, 10 were treated with primary HCT and 50 had been previously treated with imatinib. Median OS was significantly shorter with second-generation TKI treatment than with allo-HCT (22 months vs 82 months). Median progression-free and event-free survival (EFS) rates were similarly shorter with second-generation TKI treatment than with allo-HCT.

Several studies have compared outcomes for CML patients treated with allo-HCT in the pre- and current TKI eras. While these studies generally report no worsening in treatment outcomes for allo-HCT following TKI therapy, they are limited by the underlying differences in treatment regimens of different eras. In a retrospective analysis by Shen (2015), of 106 patients who underwent allo-HCT who either did (n=36) or did not (n=70) receive prior treatment with TKIs, no significant difference was reported in 10-year relapse-free survival or OS.[20] 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 to 2013; n=30), Chamseddine (2015) reported longer three-year OS and leukemia-free survival among patients treated in the TKI era.[21]

Warlick (2012) reported outcomes of 306 patients with CML treated with myeloablative or RIC preparative regimens before allogeneic HCT at the Center for International Blood and Marrow Transplant Research.[22] Although age, disease status, prior treatment (including TKI and autologous transplant), and strength of donor match differed between the treatment groups, a statistical model indicated a potential association between use of RIC preparatory regimen and increased survival (when compared with traditional myeloablative regimens). However, the lack of randomization to treatment group limits the interpretation of these findings as treatment imbalances between groups may have accounted for the differences seen in survival rates.

The optimal timing for HCT in the context of TKI therapy is still being evaluated. Liu (2013) evaluated outcomes for chronic-phase CML patients who underwent HCT after imatinib

failure.[23] The study authors retrospectively evaluated 105 patients with newly diagnosed chronic-phase CML seen at a single institution from 1999 to 2011. A total of 66 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. A total of 22 (21.0%) 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 Bone Marrow Transplantation (EBMT) risk score (p=0.03). Among patients receiving allo-HCT (n=22), 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 (median follow-up, 134 months, range, 6 to 167 months). One patient died of relapse and one of chronic GVHD among patients receiving front-line allo-HCT, with a three-year survival rate of 91.7% (95% confidence interval [CI], 29 to 38 months).

In addition to the comparative studies, 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 series of 51 patients treated with allo-HCT, 32 of whom were treated for TKI resistance or intolerance, eight-year OS and EFS were 68% and 46%, respectively.[24] A prospective series of 28 patients who underwent allo-HCT after failure of at least two TKIs reported deep molecular remission in 18 subjects.[24] However, all six patients transplanted in blast crisis died. In a smaller series, Zhao (2014) reported outcomes for 12 patients with CML with disease progression on imatinib who were primary disease and three of transplant-related complications.[25] After a median follow-up of 28 months (range, 12 to 37 months) after HCT, 8/12 (66.7%) patients were alive, including seven with complete molecular remission.

Lee (2014) attempted to identify predictors of outcomes in patients who underwent allogeneic HCT for CML in chronic phase.[26] Ninety-seven patients were included, 47 of whom were TKI-naïve and 50 of whom had received one or more TKI therapy before HCT. Most (n=48) of the TKI-recipients had received imatinib as initial therapy; two had received second-generation TKIs (dasatinib, bosutinib). After a median follow-up of 115.8 months, four-year OS and event-free survival were 80.4% and 58.8%, respectively. Multivariate analysis showed that there were no differences in survival outcomes based on prior TKI therapy. However, in multivariate models, age at transplant was significantly associated with relapse and transplant-related mortality, while graft source (peripheral blood vs bone marrow) was significantly associated with event-free survival. The authors conclude that their findings confirm prior researchers' findings that pretreatment with imatinib does not affect survival outcomes after allogeneic HCT for CML.

In addition to being used before HCT, TKI therapy may be used after HCT to prevent or treat disease relapse. Egan (2015) conducted a retrospective analysis of patients at a single institution who underwent allogeneic HCT for CML and Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL) at a single institution with detectable BCR-ABL transcripts and RNA available for sequencing of the ABL kinase domain in both the pre- and post-HCT settings to evaluate the impact of pre-HCT mutations in the ABL kinase domain on post-HCT relapse.[27] Among 95 patients with CML with available polymerase chain reaction transcripts, 10 (10.5%) were found to have pre-HCT ABL kinase mutations known to confer resistance to TKIs. Of those with CML, 88.4% underwent myeloablative chemotherapy and 11.6% underwent nonmyeloablative chemotherapy. A total of 29 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 mutations (both CML and Philadelphia

chromosome –positive ALL), the same mutation conferring TKI resistance was also detectable after HCT. Among the 14 with pre-HCT mutations, eight (57.1%) received a TKI in the post-HCT setting, and seven (50%) demonstrated post-HCT refractory disease or relapse. Of the seven with relapsed disease, five had been given a predictably ineffective TKI based on mutation status in the first 100 days after HCT. 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.[10, 17, 18]

However, the advent of TKI therapy has altered the treatment paradigm for CML such that the majority of patients are treated initially with a TKI until disease progresses. While progression may occur within months of starting a TKI, this may be delayed for years, as shown by the results of the IRIS trial[8] and other studies.[9, 10] With the addition of two other TKIs (dasatinib and nilotinib) plus the possibility of effective dose escalation with imatinib to override resistance, it is possible to maintain a typical CML patient past the upper age limit (usually 50–55 years) at which a myeloablative allogeneic HCT is considered an option.[8, 28, 29] In such cases, RIC allogeneic HCT would be considered a viable choice because it harnesses the potent GVL effect of allogeneic HCT with substantially reduced treatment-related morbidity and mortality compared to myeloablative allogeneic HCT.

AUTOLOGOUS HCT

A major limitation in the use of autologous HCT in patients with CML is the risk that leukemic cells will be re-infused. 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.[30] Even without such techniques, there have been isolated case reports of partial cytogenetic remissions after autologous HCT, and one study has suggested that patients undergoing such therapy may have improved survival compared with historical controls.[4]

In 1994, McGlave summarized the results of 200 consecutive autologous transplants using purged or unpurged marrow from eight different transplant centers.[31] 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.[4] Additional reports of small, uncontrolled studies with a total of 182 patients (range: 15 to 41 patients) given autotransplants for CML included patient populations that varied across the studies. Some focused on newly diagnosed patients or those in the first year since diagnosis.[32, 33] Others focused on patients who did not respond to or relapsed after initial treatment using interferon alfa,[34, 35] or who received interferon alfa as maintenance therapy following autologous HCT.[36] Finally, some focused on patients transplanted in the late chronic phase[37] or after transformation to accelerated phase or blast crisis.[38] Although some patients achieved complete or partial molecular remissions and long-term disease-free survival, these studies do

not permit conclusions free from the influence of patient selection bias. Note also that all autotransplanted patients included in these reports were treated before imatinib mesylate or newer TKIs became available. Since these agents have been shown to induce major hematologic and, less often, cytogenetic remissions, even among patients in accelerated phase and blast crisis, future studies of autotransplants for CML may focus on patients who fail or become resistant to imatinib mesylate. Alternatively, it may be incorporated into combination regimens used for high-dose therapy.[39]

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY FOR TRANSPLANTATION AND CELLULAR THERAPY

In 2020, guidelines by the American Society for Blood and Marrow Transplantation (now the American Society for Transplantation and Cellular Therapy) addressed indications for autologous and allogeneic HCT for CML.[40] 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.

NATIONAL COMPREHENSIVE CANCER NETWORK

Current National Comprehensive Cancer Network (NCCN) guidelines for chronic myeloid leukemia (v1.2025) recommend allogeneic HCT for those with advanced phase CML at presentation or disease progression to blast phase.[41] The guidelines also state outcomes of allogeneic HCT are dependent on age and comorbidities, donor type, and transplant center.

All recommendations are category 2A unless otherwise indicated. Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

SUMMARY

There is enough research to show that patients with chronic myelogenous leukemia (CML) may have improved overall health outcomes when treated with allogeneic hematopoietic cell transplantation (HCT) in select patient subgroups. Clinical practice guidelines based on research also recommend allogeneic HCT for CML. Thus, myeloablative conditioning

followed by allogeneic HCT may be considered medically necessary for these patients. Among patients who are not candidates for a myeloablative conditioning regimen, allogeneic HCT with a reduced-intensity conditioning (RIC) regimen may also be considered medically necessary.

When chronic myelogenous leukemia (CML) patients are considered candidates for myeloablative conditioning for allogeneic hemopoietic cell transplantation, reduced-intensity conditioning is not clinically appropriate. Therefore, allogeneic HCT is considered not medically necessary when criteria are not met.

There is not enough research to show that autologous HCT improves health outcomes in patients with chronic myelogenous leukemia (CML) over alternative treatments such as tyrosine kinase inhibitors (TKIs). Compared to alternatives, the risks associated with myeloablative autologous HCT outweigh the benefits. Therefore, autologous HCT in patients with chronic myelogenous leukemia (CML) is considered investigational.

REFERENCES

1. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2014 update on diagnosis, monitoring, and management. *American journal of hematology.* 2014;89(5):547-56. PMID: 24729196
2. Pavlu J, Szydlo RM, Goldman JM, et al. Three decades of transplantation for chronic myeloid leukemia: what have we learned? *Blood.* 2011;117(3):755-63. PMID: 20966165
3. Maziarz RT. Who with chronic myelogenous leukemia to transplant in the era of tyrosine kinase inhibitors? *Curr Opin Hematol.* 2008;15(2):127-33. PMID: 18300759
4. Bhatia R, Verfaillie CM, Miller JS, et al. Autologous transplantation therapy for chronic myelogenous leukemia. *Blood.* 1997;89(8):2623-34. PMID: 9108379
5. McGlave PB, Shu XO, Wen W, et al. Unrelated donor marrow transplantation for chronic myelogenous leukemia: 9 years' experience of the national marrow donor program. *Blood.* 2000;95(7):2219-25. PMID: 10733488
6. Weisdorf DJ, Anasetti C, Antin JH, et al. Allogeneic bone marrow transplantation for chronic myelogenous leukemia: comparative analysis of unrelated versus matched sibling donor transplantation. *Blood.* 2002;99(6):1971-7. PMID: 11877268
7. Giralt SA, Arora M, Goldman JM, et al. Impact of imatinib therapy on the use of allogeneic haematopoietic progenitor cell transplantation for the treatment of chronic myeloid leukaemia. *Br J Haematol.* 2007;137(5):461-7. PMID: 17459051
8. Fernandez HF, Kharfan-Dabaja MA. Tyrosine kinase inhibitors and allogeneic hematopoietic cell transplantation for chronic myeloid leukemia: targeting both therapeutic modalities. *Cancer Control.* 2009;16(2):153-7. PMID: 19337201
9. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med.* 2006;355(23):2408-17. PMID: 17151364
10. Apperley JF. Managing the patient with chronic myeloid leukemia through and after allogeneic stem cell transplantation. *Hematology Am Soc Hematol Educ Program.* 2006:226-32. PMID: 17124065
11. Ratko TA, Belinson SE, Brown HM, et al. Hematopoietic Stem-Cell Transplantation in the Pediatric Population [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012 Feb. Available from: http://www.ncbi.nlm.nih.gov/books/NBK84626/. PMID: 22439159

12. Gratwohl A, Pfirrmann M, Zander A, et al. Long-term outcome of patients with newly diagnosed chronic myeloid leukemia: a randomized comparison of stem cell transplantation with drug treatment. *Leukemia.* 2016;30(3):562-9. PMID: 26464170

13. Wu J, Chen Y, Hageman L, et al. Late mortality after bone marrow transplant for chronic myelogenous leukemia in the context of prior tyrosine kinase inhibitor exposure: A Blood or Marrow Transplant Survivor Study (BMTSS) report. *Cancer.* 2019;125(22):4033-42. PMID: 31412155

14. Radujkovic A, Dietrich S, Blok HJ, et al. Allogeneic Stem Cell Transplantation for Blast Crisis Chronic Myeloid Leukemia in the Era of Tyrosine Kinase Inhibitors: A Retrospective Study by the EBMT Chronic Malignancies Working Party. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation.* 2019;25(10):2008-16. PMID: 31271884

15. Chhabra S, Ahn KW, Hu ZH, et al. Myeloablative vs reduced-intensity conditioning allogeneic hematopoietic cell transplantation for chronic myeloid leukemia. *Blood Adv.* 2018;2(21):2922-36. PMID: 30396912

16. Zhang GF, Zhou M, Bao XB, et al. Imatinib Mesylate Versus Allogeneic Hematopoietic Stem Cell Transplantation for Patients with Chronic Myelogenous Leukemia. *Asian Pacific journal of cancer prevention : APJCP.* 2016;17(9):4477-81. PMID: 27797264

17. Chakrabarti S, Buyck HC. Reduced-intensity transplantation in the treatment of haematological malignancies: current status and future-prospects. *Curr Stem Cell Res Ther.* 2007;2(2):163-88. PMID: 18220901

18. Crawley C, Szydlo R, Lalancette M, et al. Outcomes of reduced-intensity transplantation for chronic myeloid leukemia: an analysis of prognostic factors from the Chronic Leukemia Working Party of the EBMT. *Blood.* 2005;106(9):2969-76. PMID: 15998838

19. Xu L, Zhu H, Hu J, et al. Superiority of allogeneic hematopoietic stem cell transplantation to nilotinib and dasatinib for adult patients with chronic myelogenous leukemia in the accelerated phase. *Frontiers of medicine.* 2015;9(3):304-11. PMID: 26100855

20. Shen K, Liu Q, Sun J, et al. Prior exposure to imatinib does not impact outcome of allogeneic hematopoietic transplantation for chronic myeloid leukemia patients: a single-center experience in china. *International journal of clinical and experimental medicine.* 2015;8(2):2495-505. PMID: 25932195

21. Chamseddine AN, Willekens C, De Botton S, et al. Retrospective Study of Allogeneic Hematopoietic Stem Cell Transplantation in Philadelphia Chromosome-Positive Leukemia: 25 Years' Experience at Gustave Roussy Cancer Campus. *Clinical lymphoma, myeloma & leukemia.* 2015;15 Suppl:S129-40. PMID: 26297265

22. Warlick E, Ahn KW, Pedersen TL, et al. Reduced intensity conditioning is superior to nonmyeloablative conditioning for older chronic myelogenous leukemia patients undergoing hematopoietic cell transplant during the tyrosine kinase inhibitor era. *Blood.* 2012;119(17):4083-90. PMID: 22408257

23. Liu YC, Hsiao HH, Chang CS, et al. Outcome of allotransplants in patients with chronic-phase chronic myeloid leukemia following imatinib failure: prognosis revisited. *Anticancer research.* 2013;33(10):4663-7. PMID: 24123046

24. Nair AP, Barnett MJ, Broady RC, et al. Allogeneic Hematopoietic Stem Cell Transplantation Is an Effective Salvage Therapy for Patients with Chronic Myeloid Leukemia Presenting with Advanced Disease or Failing Treatment with Tyrosine Kinase Inhibitors. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation.* 2015;21(8):1437-44. PMID: 25865648

25. Zhao Y, Luo Y, Shi J, et al. Second-generation tyrosine kinase inhibitors combined with stem cell transplantation in patients with imatinib-refractory chronic myeloid leukemia. *The American journal of the medical sciences.* 2014;347(6):439-45. PMID: 24553398

26. Lee SE, Choi SY, Kim SH, et al. Prognostic factors for outcomes of allogeneic stem cell transplantation in chronic phase chronic myeloid leukemia in the era of tyrosine kinase inhibitors. *Hematology.* 2014;19(2):63-72. PMID: 23684143

27. Egan DN, Beppu L, Radich JP. Patients with Philadelphia-positive leukemia with BCR-ABL kinase mutations before allogeneic transplantation predominantly relapse with the same mutation. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation.* 2015;21(1):184-9. PMID: 25300870

28. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med.* 2010;362(24):2260-70. PMID: 20525995

29. Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med.* 2010;362(24):2251-9. PMID: 20525993

30. Szatrowski TP. Progenitor cell transplantation for chronic myelogenous leukemia. *Semin Oncol.* 1999;26(1):62-6. PMID: 10073562

31. McGlave PB, De Fabritiis P, Deisseroth A, et al. Autologous transplants for chronic myelogenous leukaemia: results from eight transplant groups. *Lancet.* 1994;343(8911):1486-8. PMID: 7911185

32. Meloni G, Capria S, Vignetti M, et al. Ten-year follow-up of a single center prospective trial of unmanipulated peripheral blood stem cell autograft and interferon-alpha in early phase chronic myeloyd leukemia. *Haematologica.* 2001;86(6):596-601. PMID: 11418368

33. Podesta M, Piaggio G, Sessarego M, et al. Autografting with Ph-negative progenitors in patients at diagnosis of chronic myeloid leukemia induces a prolonged prevalence of Ph-negative hemopoiesis. *Exp Hematol.* 2000;28(2):210-5. PMID: 10706077

34. Boiron JM, Cahn JY, Meloni G, et al. Chronic myeloid leukemia in first chronic phase not responding to alpha-interferon: outcome and prognostic factors after autologous transplantation. EBMT Working Party on Chronic Leukemias. *Bone Marrow Transplant.* 1999;24(3):259-64. PMID: 10455363

35. McBride NC, Cavenagh JD, Newland AC, et al. Autologous transplantation with Philadelphia-negative progenitor cells for patients with chronic myeloid leukaemia (CML) failing to attain a cytogenetic response to alpha interferon. *Bone Marrow Transplant.* 2000;26(11):1165-72. PMID: 11149726

36. Hackanson B, Waller CF. Long-term follow-up of patients with chronic myeloid leukemia having received autologous stem cell transplantation. *Ann Hematol.* 2011;90(4):395-9. PMID: 20922524

37. Michallet M, Thiebaut A, Philip I, et al. Late autologous transplantation in chronic myelogenous leukemia with peripheral blood progenitor cells mobilized by G-CSF and interferon-alpha. *Leukemia.* 2000;14(12):2064-9. PMID: 11187894

38. Pigneux A, Faberes C, Boiron JM, et al. Autologous stem cell transplantation in chronic myeloid leukemia: a single center experience. *Bone Marrow Transplant.* 1999;24(3):265-70. PMID: 10455364

39. Mauro MJ, Deininger MW. Chronic myeloid leukemia in 2006: a perspective. *Haematologica.* 2006;91(2):152. PMID: 16461297

40. Majhail NS, Farnia SH, Carpenter PA, et al. Indications for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American Society for Blood and Marrow Transplantation. *Biology of blood and marrow transplantation : journal of the*

American Society for Blood and Marrow Transplantation. 2015;21(11):1863-9. PMID: 26256941

41. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Chronic Myeloid Leukemia. v.1.2025. [cited 8/27/2024]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf.

CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;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	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	;autologous transplantation
	38242	Allogeneic lymphocyte infusions
HCPCS	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)

Date of Origin: *May 2010*