Hematopoietic Stem-Cell Transplantation for Chronic Myelogenous Leukemia

I. Description

Hematopoietic Stem-Cell Transplantation

Hematopoietic stem-cell transplantation (HSCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole body radiation therapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT). 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 “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 HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. 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 HSCT

The conventional (“classical”) practice of allogeneic HSCT 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
Hematopoietic Stem-Cell Transplantation for Chronic Myelogenous Leukemia

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 HSCT, 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 HSCT 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 prior to undergoing bone marrow ablation. As a consequence, autologous HSCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

Reduced-Intensity Conditioning for Allogeneic HSCT

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 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 HSCT 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 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.
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. Conventional-dose regimens used for chronic-phase disease can induce multiple remissions and delay the onset of blast crisis to a median of 4–6 years. However, successive remissions are invariably shorter and more difficult to achieve than their predecessors.

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. 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 HSCT remains the only treatment capable of inducing durable remissions or cure in CML patients.

II. Criteria/Guidelines

A. Allogeneic stem-cell transplantation using a myeloablative conditioning regimen is covered as a treatment of chronic myelogenous leukemia (see Policy Guidelines).

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

C. Autologous stem-cell transplantation as a treatment of chronic myelogenous leukemia is not covered.

III. Policy Guidelines

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

B. For patients who qualify for a myeloablative allogeneic SCT on the basis of clinical status, either a myeloablative or RIC regimen may be covered.

IV. Administrative Guidelines

A. Precertification is required. To precertify, please complete HMSA's Precertification Request and mail or fax the form as indicated along with the required documentation.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic</td>
</tr>
<tr>
<td>ICD-9-CM Procedure Code</td>
<td>Description</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>38206</td>
<td>Blood derived hematopoietic progenitor cell harvesting for transplantation, per collection, autologous</td>
</tr>
<tr>
<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor</td>
</tr>
<tr>
<td>38209</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor</td>
</tr>
<tr>
<td>38210</td>
<td>Specific cell depletion with harvest, T-cell depletion</td>
</tr>
<tr>
<td>38211</td>
<td>Tumor cell depletion</td>
</tr>
<tr>
<td>38212</td>
<td>Red blood cell removal</td>
</tr>
<tr>
<td>38213</td>
<td>Platelet depletion</td>
</tr>
<tr>
<td>38214</td>
<td>Plasma (volume) depletion</td>
</tr>
<tr>
<td>38215</td>
<td>Cell concentration in plasma, mononuclear, or buffy coat layer</td>
</tr>
<tr>
<td>38220</td>
<td>Bone marrow, aspiration only</td>
</tr>
<tr>
<td>38221</td>
<td>Biopsy, needle or trocar</td>
</tr>
<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
</tr>
<tr>
<td>38240</td>
<td>Bone marrow or blood derived peripheral stem-cell transplantation; allogeneic</td>
</tr>
<tr>
<td>38241</td>
<td>Bone marrow or blood-derived peripheral stem-cell transplantation; autologous</td>
</tr>
<tr>
<td>41.00</td>
<td>Bone marrow transplant, not otherwise specified</td>
</tr>
<tr>
<td>41.01</td>
<td>Autologous bone marrow transplant without purging</td>
</tr>
<tr>
<td>41.02</td>
<td>Allogeneic bone marrow transplant with purging</td>
</tr>
<tr>
<td>41.03</td>
<td>Allogeneic bone marrow transplant without purging</td>
</tr>
<tr>
<td>41.04</td>
<td>Autologous hematopoietic stem cell transplant without purging</td>
</tr>
<tr>
<td>41.05</td>
<td>Allogeneic hematopoietic stem cell transplant without purging</td>
</tr>
<tr>
<td>41.06</td>
<td>Cord blood stem cell transplant</td>
</tr>
<tr>
<td>41.07</td>
<td>Autologous hematopoietic stem cell transplant with purging</td>
</tr>
<tr>
<td>41.08</td>
<td>Allogeneic hematopoietic stem cell transplant with purging</td>
</tr>
<tr>
<td>41.09</td>
<td>Autologous bone marrow transplant with purging</td>
</tr>
<tr>
<td>41.91</td>
<td>Aspiration of bone marrow from donor for transplant</td>
</tr>
</tbody>
</table>
V. Scientific Background

Allogeneic HSCT

Allogeneic hematopoietic stem-cell transplantation (HSCT) is the only known potentially curative therapy for chronic myelogenous leukemia (CML). It became a standard of treatment for CML in the 1980s when the graft-versus-leukemia (GVL) effect was shown to be the critical factor for long-term disease control. (1) Studies in patients with chronic phase disease who received an human leukocyte antigen (HLA)-matched sibling donor transplant had a 45–75% probability of long-term disease-free survival, while those transplanted with more advanced disease had a 15–40% long-term survival. (2) Young, good-risk patients transplanted early in the chronic phase from HLA-matched but unrelated donors had a 40–60% probability of long-term survival, although it is lower than that of similar patients transplanted from matched sibling donors. (3, 4)

CML was once the most common malignancy for which allogeneic HSCT was performed, but by 2005, it was in eighth place among hematologic transplantation indications. 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 FDA approval of imatinib in 2001. (5) 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 HSCT. (6-8) 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.
Allogeneic HSCT has continued to develop, with important advancements in the use of nonmyeloablative or reduced-intensity conditioning (RIC) preparative regimens. RIC regimens were initially conceptualized as a means to extend the use of allogeneic HSCT 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 HSCT is of particular interest for treatment of CML given the relatively pronounced susceptibility of this malignancy to the GVL effect of allogeneic hematopoietic progenitor cells following their engraftment in the host. 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. (9) Among the studies included in this review, treatment-related mortality or nonrelapse mortality (NRM) ranged from 0% at 1 year to 29% at 1 year. In the largest experience, a retrospective European Group for Blood and Marrow Transplantation (EMBT) 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). (10) Among patients transplanted in the first chronic phase (CP1), 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 HSCT. 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 HSCT. (6, 9, 10) Thus, RIC allogeneic HSCT should be considered medically necessary for CML patients who would otherwise be expected to benefit from an allogeneic HSCT.

The advent of tyrosine kinase inhibitor (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. (6, 7) With the addition of two other TKIs (nilotinib and dasatinib) 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 HSCT is considered an option. (8, 11, 12) These patients would be eligible for a RIC allogeneic HSCT.

Clinical guidelines and recommendations for management of patients with CML in the context of TKI therapy and allogeneic HSCT have been published. (13-17) They are in concordance with this policy.

**Autologous HSCT**

A major limitation in the use of autologous HSCT 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. (18) Even without such techniques, there have been isolated case reports of partial cytogenetic remissions after autologous HSCT, and one study has suggested that patients undergoing such therapy may have improved survival compared with historical controls. (2)

Another article summarized the results of 200 consecutive autologous transplants using purged or unpurged marrow from 8 different transplant centers. (19) 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. (2) 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 focused on newly diagnosed patients or those in the first year since diagnosis. (20, 21) Others focused on patients who did not respond to or relapsed after initial treatment using interferon alfa. (22, 23) Finally, some focused on patients transplanted in the late chronic phase (24) or after transformation to accelerated phase or blast crisis. (25) 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. 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. (26)

Summary

There has been a significant change in clinical transplantation practice for CML patients, particularly over the past decade subsequent to commercial introduction of three TKI agents: imatinib, dasatinib, and nilotinib. (17) The TKIs have replaced allogeneic HSCT as initial therapy in patients with chronic phase CML. (15) However a significant proportion of cases fail to respond to TKIs, develop resistance to them, or become unable to tolerate all TKIs and go on to allogeneic HSCT. Allogeneic HSCT represents the only potentially curative option for those patients in accelerated or blast phase. (16) Given the successes seen with TKIs in chronic phase CML, and the risks associated with myeloablative autologous HSCT, the latter has declined in use to the extent that few anecdotal reports have been published since the TKI era began. (16)

National Comprehensive Cancer Network (NCCN) Guidelines

patients who do not achieve hematologic remission after 3 months of imatinib therapy
- patients with no cytogenetic response or those in cytogenetic relapse at 6, 12, or 18 months, after achieving initial hematologic remission after 3 months of imatinib therapy
- patients progressing on a TKI to accelerated phase or blast crisis.

Autologous bone marrow transplant for CML is not addressed in the NCCN guidelines.

National Cancer Institute (NCI) Clinical Trial Database (PDQ®)

A search of the National Cancer Institute clinical trial database (PDQ®) identified 11 active Phase II/III trials in the U.S. including allografting, using various conditioning regimens, as well as different stem-cell sources and mobilization protocols. (Available online at: http://www.cancer.gov/search/ResultsClinicalTrials.aspx?protocolsearchid=7038344).

VI. 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.

VII. References

22. 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
27. Blue Cross Blue Shield Association. Hematopoietic Stem-Cell Transplantation for Chronic Myelogenous Leukemia. 8.01.30; December 2011.