Protocol

Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia

(80130)

(Formerly Hematopoietic Stem Cell Transplantation for Chronic Myelogenous Leukemia)

Medical Benefit		**Effective Date**: 04/01/13	**Next Review Date**: 03/18
Preauthorization	Yes	**Review Dates**: 04/07, 05/08, 03/10, 03/11, 03/12, 03/13, 03/14, 03/15, 03/16, 03/17	

Preauthorization is required and must be obtained through Case Management.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

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

Description

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

Summary of Evidence

For individuals who have 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.

Policy

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

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

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

Policy Guidelines

Individual transplant facilities may have their own additional requirements or protocols that must be met in order for the patient to be eligible for a transplant at their facility.

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for RIC allo-HCT. 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 score) preclude use of a standard myeloablative conditioning regimen.

For patients who qualify for a myeloablative allo-HCT on the basis of clinical status, either a myeloablative or RIC regimen may be considered medically necessary.

Medicare Advantage

If a transplant is needed, we arrange to have the transplant center review and decide whether the patient is an appropriate candidate for the transplant.

Background

Hematopoietic Cell Transplantation

HCT 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 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). Cord blood is discussed in greater detail in the Placental and Umbilical Cord Blood as a Source of Stem Cells Protocol.

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 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 (antigen-D related) loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

Conditioning for HCT

CONVENTIONAL PREPARATIVE CONDITIONING FOR HCT

The conventional ("classical") practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to 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 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 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 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 of the patient to opportunistic infections. The immune reactivity between donor T cells and malignant cells that is responsible for the GVM effect also leads to acute and chronic GVHD.

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

REDUCED-INTENSITY CONDITIONING FOR ALLO-HCT

RIC refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden but also to minimize as much as possible associated treatment-related morbidity and nonrelapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with 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 the purposes of this protocol, RIC will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

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

Chronic Myeloid Leukemia

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, 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 one to two 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 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 four to six years. However, successive remissions are invariably shorter and more difficult to achieve than their predecessors.

Therapy for CML

Historically, the only curative therapy for CML in blast phase was allo-HCT, which was used more widely earlier in the disease process given the lack of other therapies for chronic phase CML. Drug therapies for chronic phase CML were limited to nonspecific agents including busulfan, hydroxyurea, and interferon-α.[1]

Imatinib mesylate (Gleevec®), a selective inhibitor of the abnormal *BCR-ABL* 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 two years and 80% to 90% at five years.[2]

For CML two other TKIs (dasatinib, nilotinib) have received marketing approval from the U.S. Food and Drug Administration (FDA) as front-line therapy or following failure or patient intolerance of imatinib. Two additional TKIs, bosutinib and 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* mutations may be important in determining an alternative TKI; the presence of *T315I* mutation 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.

Regulatory Status

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation (CFR) title 21, parts 1270 and 1271.[3] Hematopoietic stem cells are included in these regulations.

Related Protocols

Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia

Hematopoietic Stem Cell Transplantation for Non-Hodgkin Lymphomas

Placental and Umbilical Cord Blood as a Source of Stem Cells

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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