Protocol

Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia

(80126)

Medical Benefit		**Effective Date**: 07/01/16	**Next Review Date**: 05/18
Preauthorization	Yes	**Review Dates**: 04/07, 05/08, 05/09, 05/10, 05/11, 05/12, 05/13, 05/14, 05/15, 05/16, 05/17	

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 documented cytogenetic or molecular intermediate- or poor-risk AML in first complete remission	Interventions of interest are: • Allogeneic HSCT with myeloablative conditioning	Comparators of interest are: • Conventional chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival
Individuals: • With AML refractory to standard induction chemotherapy but which can be brought into first complete remission or beyond with intensified induction	Interventions of interest are: • Allogeneic HSCT with myeloablative conditioning	Comparators of interest are: • Conventional chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival
Individuals: • With AML that relapses after induction chemotherapy-induced CR1 but which can be brought into second complete remission or beyond with intensified induction chemotherapy	Interventions of interest are: • Allogeneic HSCT with myeloablative conditioning	Comparators of interest are: • Conventional chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival
Individuals: • With documented cytogenetic or molecular intermediate- or poor-risk AML in first complete remission or beyond, who for medical reasons cannot tolerate a myeloablative conditioning	Interventions of interest are: • Allogeneic HSCT with reduced-intensity conditioning	Comparators of interest are: • Myeloablative conditioning allogeneic HSCT • Conventional chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Treatment-related morbidity
Individuals: • With AML in first complete remission or beyond who do not have a suitable allogeneic HSCT	Interventions of interest are: • Autologous HSCT	Comparators of interest are: • Conventional chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival

AML: acute myeloid leukemia; HSCT: hematopoietic stem cell transplantation.

Description

Acute myeloid leukemia (AML) refers to leukemias that arise from a myeloid precursor in the bone marrow. There is a high incidence of relapse, which has prompted research into various postremission strategies using either allogeneic (allo) or autologous hematopoietic stem cell transplantation (HSCT). HSCT refers to a procedure that infuses hematopoietic stem cells to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs with or without whole body radiotherapy.

Summary of Evidence

The evidence for allogeneic hematopoietic stem cell transplantation (allo-HSCT) with myeloablative conditioning in individuals who have cytogenetic or molecular intermediate- or poor-risk AML in first complete remission includes randomized controlled trials (RCTs) and matched cohort studies. Relevant outcomes are overall survival and disease-specific survival. The evidence shows allo-HSCT in this setting improves overall and disease-specific survival rates better than conventional chemotherapy. All trials employed natural randomization based on donor availability and an intention-to-treat analysis. Although the selected studies used a range of definitions of risk categories produced by different cooperative groups (e.g., SWOG, Medical Research Council, European Organisation for Research and Treatment of Cancer, Gruppo Italiano Malattie Ematologiche dell' Adulto), cyto-genetic categories in those definitions are very similar to recent guidelines from the National Comprehensive Cancer Network.

The evidence for allo-HSCT with myeloablative conditioning in individuals who have AML refractory to induction chemotherapy or relapses after autologous HSCT but can be brought into remission with intensified chemothe-rapy includes retrospective data compiled from patients entered in phase three trials and registry data. Relevant outcomes are overall survival and disease-specific survival. The evidence suggests allo-HSCT in this setting improves overall and disease-specific survival rates better than conventional chemotherapy. Limitations of the evidence include its retrospective nature, lack of rigorous randomization, and pitfalls of registry data.

The evidence for allo-HSCT with myeloablative conditioning in individuals who have AML in second complete remission and beyond includes retrospective data compiled from patients entered in phase three trials and registry data. Relevant outcomes are overall survival and disease-specific survival. The evidence shows allo-geneic HSCT in this setting improves overall survival (OS) rates better than conventional chemotherapy. Limitations of the evidence include its retrospective nature, lack of rigorous randomization, and pitfalls of registry data.

The evidence for allo-HSCT with reduced-intensity conditioning (RIC) in individuals who have AML in first com-plete remission or beyond and who otherwise would be candidates for an allogeneic transplant includes RCT and other comparative studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity. RIC with allo-HSCT has not been directly compared with conventional chemotherapy, which is the standard of care in patients with AML for whom myeloablative chemotherapy and allo-HSCT are contraindi-cated. Indirect comparison of results from nonrandomized studies or comparative studies is compromised by heterogeneity among patients, treatments, outcome measures, and insufficient follow-up. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for autologous HSCT in individuals who have AML in first complete remission or beyond but do not have a suitable allogeneic donor includes prospective cohort studies in which patients with an available sibling donor were offered allo-HSCT (biologic randomization) with random assignment of all others to autologous HSCT or chemotherapy (or no further treatment); and randomized trials comparing autologous HSCT to chemotherapy

in all patients. Relevant outcomes are overall survival and disease-specific survival. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

Policy

Allogeneic hematopoietic stem-cell transplantation (HSCT) using a myeloablative conditioning regimen may be considered **medically necessary** to treat:

- poor- to intermediate-risk AML in first complete remission (CR1) (see Policy Guidelines for information on risk stratification), or
- AML that is refractory to standard induction chemotherapy but can be brought into CR with intensified induction chemotherapy; or
- AML that relapses following chemotherapy-induced CR1 but can be brought into CR2 or beyond with intensified induction chemotherapy; or
- AML in patients who have relapsed following a prior autologous HSCT but can be brought into CR with intensified induction chemotherapy and are medically able to tolerate the procedure.

Allogeneic HSCT using a reduced-intensity conditioning regimen may be considered **medically necessary** as a treatment of AML in patients who are in complete marrow and extramedullary remission (CR1 or beyond), and who for medical reasons would be unable to tolerate a myeloablative conditioning regimen (see Policy Guidelines).

Autologous HSCT may be considered **medically necessary** to treat AML in CR1 or beyond, or relapsed AML, if responsive to intensified induction chemotherapy.

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.

Primary refractory AML is defined as leukemia that does not achieve a complete remission after conventionally dosed (non-marrow ablative) chemotherapy.

In the French-American-British (FAB) criteria, the classification of AML is solely based on morphology as determined by the degree of differentiation along different cell lines and the extent of cell maturation.

Clinical features that predict poor outcomes of AML therapy include, but are not limited to, the following:

- Treatment-related AML (secondary to prior chemotherapy and/or radiotherapy for another malignancy)
- AML with antecedent hematologic disease (e.g., myelodysplasia)
- Presence of circulating blasts at the time of diagnosis
- Difficulty in obtaining first complete remission with standard chemotherapy
- Leukemias with monocytoid differentiation (FAB classification M4 or M5).

The newer, currently preferred, World Health Organization (WHO) classification of AML incorporates and interrelates morphology, cytogenetics, molecular genetics, and immunologic markers. It attempts to construct a classification that is universally applicable and prognostically valid. The WHO system was adapted by the

National Comprehensive Cancer Network (NCCN) to estimate individual patient prognosis to guide management, as shown in the following table.

Risk Status of Acute Myeloid Leukemia Based on Cytogenetic and Molecular Factors

Risk Status	Cytogenetic Factors	Molecular Abnormalities
Favorable	Inv(16), t(8;21), t(16;16)	Normal cytogenetics with isolated NPM1 mutation
Intermediate	Normal +8 only, t(9;11) only Other abnormalities not listed with better-risk and poor-risk cytogenetics	c-KIT mutation in patients with t(8;21) or inv(16)
Poor	Complex (three or more abnormalities) -5, -7, 5q-, 7q-, +8, Inv3, t(3;3), t(6;9), t(9;22) Anormalités of 11q23, excluding t(9;11)	Normal cytogenetics with isolated FLT3-ITD mutations

The relative importance of cytogenetic and molecular abnormalities in determining prognosis and guiding therapy is under investigation.

The ideal allogeneic donors are HLA-identical siblings, matched at the HLA-A, -B, and -DR loci (six of six). Related donors mismatched at one locus are also considered suitable donors. A matched, unrelated donor identified through the National Marrow Donor Registry is typically the next option considered. Recently, there has been interest in haploidentical donors, typically a parent or a child of the patient, for which there usually is sharing of only three of the six major histocompatibility antigens. Most patients will have such a donor; however, the risk of graft-versus-host disease and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

Medicare Advantage

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

Background

Hematopoietic Stem Cell Transplantation

HSCT may use stem cells obtained from the transplant recipient (autologous HSCT) or from a related or unrelated donor (allo-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 “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 HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allo-HSCT. Compatibility is established by typing of human leukocyte antigen (HLA) 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).

Complete remissions can be achieved initially using conventional doses of combination chemotherapy in up to 80% of AML patients. However, the high incidence of disease relapse has prompted research into a variety of postremission (consolidation) strategies, typically using high-dose chemotherapy with autologous HSCT or high-dose or reduced-intensity chemotherapy with allo-HSCT. As outlined next, the two treatments–autologous HSCT and allo-HSCT–represent two different strategies. The first, autologous HSCT, is a "rescue," but not a therapeutic procedure; the second, allo-HSCT, is a "rescue" plus a therapeutic procedure.

Conventional Preparative Conditioning for HSCT

The conventional ("classical") practice of allo-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 this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect 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-HSCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increase the patient's susceptibility 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 before 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 Allo-HSCT

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-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 this protocol, the term RIC will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

Acute Myeloid Leukemia

AML (also called acute nonlymphocytic leukemia) refers to a set of leukemias that arise from a myeloid precursor in the bone marrow. AML is characterized by proliferation of myeloblasts, coupled with low production of mature red blood cells, platelets, and often non–lymphocytic white blood cells (granulocytes, monocytes). Clinical signs and symptoms are associated with neutropenia, thrombocytopenia, and anemia. The incidence of AML increases with age, with a median of 67 years. Approximately 13,000 new cases are diagnosed annually.

The pathogenesis of AML is unclear. It can be subdivided according to resemblance to different subtypes of normal myeloid precursors using the French-American-British (FAB) classification system. This system classifies leukemias from M0–M7, based on morphology and cytochemical staining, with immunophenotypic data in some instances. The World Health Organization (WHO) subsequently incorporated clinical, immunophenotypic, and a wide variety of cytogenetic abnormalities that occur in 50% to 60% of AML cases into a classification system that can be used to guide treatment according to prognostic risk categories.

The WHO system recognizes five major subcategories of AML: (1) AML with recurrent genetic abnormalities; (2) AML with multilineage dysplasia; (3) therapy-related AML and myelodysplasia; (4) AML not otherwise categorized; and (5) acute leukemia of ambiguous lineage. AML with recurrent genetic abnormalities includes AML with t(8;21)(q22;q22), inv(16)(p13:q22) or t(16;16)(p13;q22), t(15;17)(q22;q12), or translocations or structural abnormalities involving 11q23. Younger patients may exhibit t(8;21) and inv(16) or t(16;16). AML patients with 11q23 translocations include two subgroups: AML in infants and therapy-related leukemia. Multilineage dysplasia AML must exhibit dysplasia in 50% or more of the cells of two lineages or more, which is associated with cytogenetic findings that include -7/del(7q), -5/del(5q), +8, +9, +11, del(11q), del(12p), -18, +19, del(20q)+21, and other translocations. AML not otherwise categorized includes disease that does not fulfill criteria for the other groups and essentially reflects the morphologic and cytochemical features and maturation level criteria used in the FAB classification, except for the definition of AML as having a minimum of 20% (as opposed to 30%) blasts in the marrow. AML of ambiguous lineage is diagnosed when blasts lack sufficient lineage-specific antigen expression to classify as myeloid or lymphoid.

Molecular studies have identified a number of genetic abnormalities that also can be used to guide prognosis and management of AML. Cytogenetically normal AML (CN-AML) is the largest defined subgroup of AML, comprising approximately 45% of all AML cases. Despite the absence of cytogenetic abnormalities, these cases often have genetic mutations that affect outcomes, six of which have been identified. The *FLT3* gene that encodes FMS-like receptor tyrosine kinase (TK) 3, a growth factor active in hematopoiesis, is mutated in 33% to 49% of CN-AML cases; among those, 28% to 33% consist of internal tandem duplications (ITD), 5% to 14% are missense mutations in exon 20 of the TK activation loop, and the rest are point mutations in the juxtamembrane domain. All *FLT3* mutations result in a constitutively activated protein and confer a poor prognosis. Several pharmaceutic agents that inhibit the *FLT3* TK are under investigation.

Regulatory Status

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

Related Protocol

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.**

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

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