Protocol

Hematopoietic Cell Transplantation for Acute Myeloid Leukemia

(80126)

Medical Benefit		**Effective Date**: 08/01/19	**Next Review Date**: 05/21
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, 05/18, 05/19, 05/20	

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 cytogenetic or molecular intermediate- or poor-risk acute myeloid leukemia in first complete	Interventions of interest are: • Allogeneic hematopoietic cell transplantation with myeloablative conditioning	Comparators of interest are: • Conventional chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival
Individuals: • With acute myeloid leukemia refractory to standard induction chemotherapy	Interventions of interest are: • Allogeneic hematopoietic cell transplantation with myeloablative conditioning	Comparators of interest are: • Conventional chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival
Individuals: • With acute myeloid leukemia who relapsed after standard induction chemotherapy-induced first complete remission	Interventions of interest are: • Allogeneic or autologous hematopoietic cell transplantation with myeloablative conditioning	Comparators of interest are: • Conventional chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival
Individuals: • With cytogenetic or molecular intermediate- or poor-risk acute myeloid leukemia in remission and cannot tolerate myeloablative conditioning	Interventions of interest are: • Allogeneic hematopoietic cell transplantation with reduced-intensity conditioning	Comparators of interest are: • Myeloablative conditioning allogeneic hematopoietic cell transplantation • Conventional chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Treatment-related morbidity
Individuals: • With acute myeloid leukemia in remission without suitable allogeneic hematopoietic cell transplantation donor	Interventions of interest are: • Autologous hematopoietic cell transplantation	Comparators of interest are: • Conventional chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival

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 post-remission strategies using either allogeneic (allo-) or autologous hematopoietic cell transplantation (HCT). HCT 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

For individuals who have cytogenetic or molecular intermediate- or poor-risk AML in first complete remission (CR1) who receive allo-HCT with myeloablative conditioning (MAC), the evidence includes RCTs and matched cohort studies. The relevant outcomes are overall survival (OS) and disease-specific survival (DSS). The evidence has revealed that allo-HCT is better at improving OS and DSS rates in patients with AML in CR1 than conventional chemotherapy. All trials employed natural randomization based on donor availability and intention-to-treat analysis. Survival rates appear to be associated with the presence of minimal residual disease and risk category. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have AML refractory to standard induction chemotherapy who receive allo-HCT with MAC, the evidence includes retrospective data compiled from patients entered in phase three trials and registry data. The relevant outcomes are OS and DSS. The evidence would suggest that allo-HCT improves OS and DSS rates in patients who are refractory to induction chemotherapy better than conventional chemotherapy. While there are some limitations to the evidence, which include its retrospective nature, lack of rigorous randomization, and general pitfalls of registry data, these results may provide a clinically meaningful benefit for patients who do not have other treatment options. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have AML who relapsed after standard induction chemotherapy-induced CR1 who receive allo-HCT or autologous HCT with MAC, the evidence includes retrospective data compiled from patients entered in phase three trials and registry data. The relevant outcomes are OS and DSS. The evidence has shown that allo-HCT improves OS rates in patients with relapsed AML better than conventional chemotherapy. Limitations of the evidence include its retrospective nature, lack of rigorous randomization, and pitfalls of registry data. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have cytogenetic or molecular intermediate- or poor-risk AML in CR1 and for medical reasons cannot tolerate MAC who receive allo-HCT with reduced-intensity conditioning, the evidence includes two RCTs, two meta-analyses, and other comparative and noncomparative studies. The relevant outcomes are OS, DSS, and treatment-related morbidity. The RCTs compared reduced-intensity conditioning with MAC and reported similar rates in non-relapse mortality, relapse, and OS though one of the trials was stopped prematurely due to slow accrual of patients. Two retrospective comparative studies found no difference in OS or leukemia-free survival between the conditioning regimens. It appears unlikely that additional comparative evidence will be generated. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have AML in CR1 for beyond without a suitable allo-HCT donor who receives autologous HCT, the evidence includes prospective cohort studies in which patients with an available sibling donor were offered allo-HCT (biologic randomization) with random assignment of all others to autologous HCT or chemotherapy (or no further treatment); and randomized trials comparing autologous HCT with chemotherapy in all patients. The relevant outcomes are OS and DSS. Compared with chemotherapy, patients undergoing autolo-

gous HCT experienced reduced relapse and improved disease-free survival rates. The OS did not differ between the groups. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

POLICY

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

- poor- to intermediate-risk acute myeloid leukemia (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 HCT but can be brought into CR with intensified induction chemotherapy and are medically able to tolerate the procedure.

Allogeneic HCT 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 HCT may be considered **medically necessary** to treat AML in CR1 or beyond, or relapsed AML, if responsive to intensified induction chemotherapy in patients who are not candidates for allogeneic HCT.

Allogeneic and autologous HCT are **investigational** in patients not meeting any of the above criteria.

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 clas-

sification 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 AML 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 variant
Intermediate	Normal +8 only, t(9;11) only Other abnormalities not listed with better-risk and poor-risk cytogenetics	c-KIT variant in patients with t(8;21) or inv16
Poor	Complex (three or more abnormalities) -5, -7, 5q-, 7q-, +8, Inv3, t(3;3), t(6;9), t(9;22) Abnormalities of 11q23, excluding t(9;11)	Normal cytogenetics with isolated FLT3-ITD variant

AML: acute myeloid leukemia; ITD: internal tandem duplication

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

The ideal allogeneic donors are human leukocyte antigen (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

TREATMENT

Complete remission can be achieved initially using induction therapy, consisting of conventional doses of combination chemotherapy. A complete response is achieved in 60% to 80% of adults younger than 60 years of age and 40% to 60% in patients older than 60 years of age. However, the high incidence of disease relapse has prompted research into a variety of post-remission (consolidation) strategies, typically using high-dose chemotherapy with autologous hematopoietic cell transplantation (HCT) or high-dose or reduced-intensity chemotherapy with allogeneic HCT (allo-HCT). The two treatments – autologous HCT and allo-HCT – represent two different strategies. The first, autologous HCT, is a “rescue,” but not a therapeutic procedure; the second, allo-HCT, is a “rescue” plus a therapeutic procedure.

Hematopoietic Cell Transplantation

HCT is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune function in cancer patients who receive bone marrow-toxic doses of cytotoxic drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allo-HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood

shortly after delivery of neonates. Cord blood transplantation is discussed in 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. In allogeneic stem cell transplantation, immunologic compatibility between donor and patient is a critical factor for achieving a successful outcome. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. An acceptable donor will match the patient at all or most of the HLA loci.

Conditioning for Hematopoietic Cell Transplantation

Conventional Conditioning

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 cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of the initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease, which increases susceptibility to opportunistic infections.

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

Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation

RIC refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. RIC regimens range from nearly total myeloablative to minimally myeloablative with lympho-ablation, 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. In this review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative.

A 2015 review in the New England Journal of Medicine summarized recent advances in the classification of acute myeloid leukemia, the genomics of acute myeloid leukemia and prognostic factors, and current and new treatments.[1]

REGULATORY STATUS

The FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the

Center for Biologics Evaluation and Research, under Code of Federal Regulation, Title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

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 and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services 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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