**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.

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With cytogenetic or molecular intermediate- or poor-risk acute myeloid</td>
<td>• Allogeneic hematopoietic cell transplantation with myeloablative conditioning</td>
<td>• Conventional chemotherapy</td>
<td>• Overall survival</td>
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<tr>
<td>leukemia in first complete</td>
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<td></td>
<td>• Disease-specific survival</td>
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<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
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</tr>
<tr>
<td>• With acute myeloid leukemia refractory to standard induction chemotherapy</td>
<td>• Allogeneic hematopoietic cell transplantation with myeloablative conditioning</td>
<td>• Conventional chemotherapy</td>
<td>• Overall survival</td>
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<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With acute myeloid leukemia who relapsed after standard induction</td>
<td>• Allogeneic or autologous hematopoietic cell transplantation with myeloablative conditioning</td>
<td>• Conventional chemotherapy</td>
<td>• Overall survival</td>
</tr>
<tr>
<td>chemotherapy-induced first complete remission</td>
<td></td>
<td></td>
<td>• Disease-specific survival</td>
</tr>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With cytogenetic or molecular intermediate- or poor-risk acute myeloid</td>
<td>• Allogeneic hematopoietic cell transplantation with reduced-intensity</td>
<td>• Myeloablative conditioning</td>
<td>• Overall survival</td>
</tr>
<tr>
<td>leukemia in remission and cannot tolerate myeloablative conditioning</td>
<td>conditioning</td>
<td>• Allogeneic hematopoietic cell transplantation</td>
<td>• Disease-specific survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Conventional chemotherapy</td>
<td>• Treatment-related morbidity</td>
</tr>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With acute myeloid leukemia in remission without suitable allogeneic</td>
<td>• Autologous hematopoietic cell transplantation</td>
<td>• Conventional chemotherapy</td>
<td>• Overall survival</td>
</tr>
<tr>
<td>hematopoietic cell transplantation donor</td>
<td></td>
<td></td>
<td>• Disease-specific survival</td>
</tr>
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</table>
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 who receive allo-HCT with MAC, the evidence includes randomized controlled trials (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 first complete remission 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 (MRD) 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 3 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 first complete remission who receive allo-HCT or autologous HCT with MAC, the evidence includes retrospective data compiled from patients entered in phase 3 trials and registry data. 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 first complete remission and for medical reasons cannot tolerate MAC who receive allo-HCT with reduced-intensity conditioning (RIC), 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 nonrelapse 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 first complete remission or 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 autologous 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 inter-relates 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 AML Based on Cytogenetic and Molecular Factors**

<table>
<thead>
<tr>
<th>Risk Status</th>
<th>Cytogenetic Factors</th>
<th>Molecular Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>Inv(16), t(8;21), t(16;16)</td>
<td>Normal cytogenetics with isolated NPM1 variant</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Normal</td>
<td>c-KIT variant in patients with t(8;21) or inv16</td>
</tr>
<tr>
<td></td>
<td>+8 only, t(9;11) only</td>
<td>Other abnormalities not listed with better-risk and poor-risk cytogenetics</td>
</tr>
<tr>
<td>Poor</td>
<td>Complex (three or more abnormalities)</td>
<td>Normal cytogenetics with isolated FLT3-ITD variant</td>
</tr>
<tr>
<td></td>
<td>-5, -7, 5q-, 7q-, +8, inv3, t(3;3), t(6;9), t(9;22)</td>
<td>Abnormalities of 11q23, excluding t(9;11)</td>
</tr>
</tbody>
</table>

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**

**ACUTE MYELOID LEUKEMIA**

AML, also called acute nonlymphocytic leukemia, AML refers to a set of leukemias that arise from a myeloid precursor in the bone marrow. AML is characterized by a 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 21380 new cases are diagnosed annually.

**Pathophysiology**

The pathogenesis of AML is unclear. It can be subdivided by similarity to different subtypes of normal myeloid...
precursors using the FAB classification system. This system classifies leukemias from M0 to M7, based on morphology and cytochemical staining, with immunophenotypic data in some instances. The 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.

Classification

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), inv16(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 inv16 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 or more lineages, which is associated with cytogenetic findings that include --5, 5q-, -7, 7q-, +8, +9, +11, 11q-, 12p-, -18, +19, 20q-, +21, and other translocations. AML not otherwise categorized includes a 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.

Genetic Abnormalities

Molecular studies have identified a number of genetic abnormalities that can also be used to guide prognosis and management of AML. Cytogenetically normal 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 variants that affect outcomes, six of which have been identified. The FLT3 gene that encodes FMS-like receptor tyrosine kinase 3, a growth factor active in hematopoiesis, is mutated in 33% to 49% of cytogenetically normal AML cases; among those, 28% to 33% consist of internal tandem duplications, 5% to 14% are missense variants in exon 20 of the tyrosine kinase activation loop, and the rest are single nucleotide variants in the juxtamembrane domain. All FLT3 variants result in a constitutively activated protein and confer a poor prognosis. Several pharmaceutic agents that inhibit the FLT3 tyrosine kinase are under investigation.

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 HCT or high-dose or reduced-intensity chemotherapy with 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 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 (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 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 critical for achieving a good outcome with allo-HCT. Immunologic compatibility is established by classifying 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 (with the exception of umbilical cord blood).

Conventional Conditioning for HCT

The conventional practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation; this is performed at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect of 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 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 medically fit to tolerate substantial adverse events 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 allo-HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increase susceptibility to opportunistic infections. The immune reactivity between donor T-cells and malignant cells is responsible for the GVM effect; it 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 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 two-fold: to reduce disease burden, and to minimize treatment-related morbidity and nonrelapse mortality when 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 nonrelapse mortality and relapse due to residual disease. RIC regimens can be viewed as a continuum—from nearly totally myeloablative to minimally myeloablative with lymphoablation—because it tailors its intensity 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 this protocol, RIC refers to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

A 2015 review in the New England Journal of Medicine has summarized recent advances in the classification of AML, the genomics of AML and prognostic factors, and current and new treatments.\(^2\)

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, title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.
RELATED PROTOCOLS
Genetic Testing for Leukemia and Lymphoma
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.


