Hematopoietic Cell Transplantation for Acute Myeloid Leukemia

Policy #  00049
Original Effective Date: 01/28/2002
Current Effective Date: 11/15/2017

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Allogeneic Hematopoietic Cell Transplant
Based on review of available data, the Company may consider allogeneic hematopoietic cell transplant (allo-HCT) using a myeloablative conditioning (MAC) regimen to treat acute myeloid leukemia (AML) to be eligible for coverage.

Patient Selection Criteria
Coverage eligibility will be considered for allogeneic hematopoietic cell transplant (allo-HCT) using a myeloablative conditioning (MAC) regimen to treat acute myeloid leukemia (AML) when ANY of the following criteria are met:

- Poor-to intermediate-risk acute myeloid leukemia (AML) in first complete remission (CR1) (see Policy Guidelines section for information on risk stratification); OR
- Acute myeloid leukemia (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 complete remission 1 (CR1) but can be brought into CR2 or beyond with intensified induction chemotherapy; OR
- Acute myeloid leukemia (AML) in patients who have relapsed following a prior autologous hematopoietic cell transplant (HCT), but can be brought into complete remission (CR) with intensified induction chemotherapy and are medically able to tolerate the procedure.

Based on review of available data, the Company may consider allogeneic hematopoietic cell transplant (allo-HCT) using a reduced-intensity conditioning (RIC) regimen as a treatment of acute myeloid leukemia (AML) in patients who are in complete marrow and extramedullary remission, and who for medical reasons would be unable to tolerate a myeloablative conditioning (MAC) regimen to be eligible for coverage (see Policy Guidelines section).

Autologous Hematopoietic Cell Transplant
Based on review of available data, the Company may consider autologous hematopoietic cell transplant (HCT) to treat acute myeloid leukemia (AML) in first complete remission (CR1) or beyond, or relapsed acute myeloid leukemia (AML) if responsive to intensified induction of chemotherapy to be eligible for coverage.
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When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of allogeneic hematopoietic cell transplant (allo-HCT) when patient selection criteria are not met to be investigational.*

Policy Guidelines

Primary refractory acute myeloid leukemia (AML) is defined as leukemia that does not achieve a complete remission (CR) after conventionally dosed (nonmarrow 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 (CR1) 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 National Comprehensive Cancer Network (NCCN) to estimate individual patient prognosis to guide management, as shown in Table PG1.

<table>
<thead>
<tr>
<th>Risk Status</th>
<th>Cytogenetic Factors</th>
<th>Molecular Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>Inv16, (t;8;21), t(16;16)</td>
<td>Normal cytogenetics with isolated NPM1 variant</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Normal +8 only, t(9;11) only</td>
<td>c-KIT variant in patients with t(8;21) or inv(16)</td>
</tr>
<tr>
<td></td>
<td>Other abnormalities not listed with better-risk and poor-risk cytogenetics</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>Complex (≥3 abnormalities) -5, -7, 5q-, 7q-, +8, inv(3), t(3;3), t(6;9), t(9;22) Abnormalities of 11q23, excluding t(9;11)</td>
<td>Normal cytogenetics with isolated FLT3-ITD variant</td>
</tr>
</tbody>
</table>

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.

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The ideal allogeneic donors are human leukocyte antigen (HLA)–identical siblings, matched at the HLA-A, -B, and -DR loci (6 of 6). Related donors mismatched at 1 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 3 of the 6 major histocompatibility antigens. Most patients will have such a donor; however, the risk of graft-versus-host disease (GVHD) and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

**Background/Overview**

**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 (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 GVHD.

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 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 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 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 CR. 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 MAC treatments. The goal of RIC is 2-fold: to reduce disease burden, and to minimize treatment-related morbidity and nonrelapse mortality 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 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 evidence review, RIC refers 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.

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 5 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 inv16 or
t(16;16). AML patients with 11q23 translocations include 2 subgroups: AML in infants and therapy-related leukemia. Multilineage dysplasia AML must exhibit dysplasia in 50% or more of the cells of 2 lineages or more, 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 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.

**Treatment**

Molecular studies have identified a number of genetic abnormalities that also can 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 (SNVs) in the juxtamembrane domain. All *FLT3* variants result in a constitutively activated protein and confer a poor prognosis. Several pharmacologic agents that inhibit the *FLT3* tyrosine kinase are under investigation.

CR 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 in 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 postremission (consolidation) strategies, typically using high-dose chemotherapy with autologous HCT or high-dose or reduced-intensity chemotherapy with allo-HCT. The 2 treatments—autologous HCT and allo-HCT—represent 2 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.

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)

The U.S. 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.

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.
Rationale/Source
HCT has been investigated as consolidation therapy for patients whose disease enters CR following initial induction treatment. It also is used as salvage therapy in patients who experience disease relapse or have disease refractory to induction chemotherapy. This evidence review discusses the following uses and conditions of HCT: consolidation therapy with allo-HCT during CR1, salvage therapy for refractory AML, therapy for relapsed AML, RIC, and consolidation therapy with autologous HCT.

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.

**ALLOGENEIC HCT FOR CHEMOTHERAPY-RESPONSIVE CONSOLIDATION**

**Systematic Reviews**
A 2015 meta-analysis examined prospective trials of adults with intermediate-risk AML in CR1 who underwent HCT. The analysis included 9 prospective, controlled studies that enrolled 1950 patients between the years 1987 and 2011 (size range, 32-713 patients). Allo-HCT was associated with significantly better relapse-free survival, overall survival (OS), and relapse rate than autologous HCT and/or chemotherapy (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.48 to 0.95; HR=0.76; 95% CI, 0.61 to 0.95; HR=0.58; 95% CI, 0.45 to 0.75, respectively). Treatment-related mortality was significantly higher following allo-HCT than autologous HCT (HR=3.09; 95% CI, 1.38 to 6.92). However, a subgroup analysis, which used updated criteria to define intermediate-risk AML, showed no OS benefit for allo-HCT over autologous HCT (HR=0.99; 95% CI, 0.70 to 1.39).

A 2009 systematic review incorporated data from 24 trials involving 6007 patients who underwent allo-HCT in CR1. Among the total, 3638 patients were stratified and analyzed according to cytogenetic risk (547 good-, 2499 intermediate-, 592 poor-risk patients with AML) using a fixed-effects model. Compared with either autologous HCT or additional consolidation chemotherapy, the HR for OS among poor-risk patients across 14 trials was 0.73 (95% CI, 0.59 to 0.90; p<0.01); among intermediate-risk patients across 14 trials, the HR for OS was 0.83 (95% CI, 0.74 to 0.93; p<0.01); and among good-risk patients across 16 trials, the HR for OS was 1.07 (95% CI, 0.83 to 1.38; p=0.59). Interstudy heterogeneity was not significant in any of these analyses. Results for DFS were very similar to those for OS in this analysis. These results concur with those from another meta-analysis on the use of allo-HCT as consolidation therapy for AML.

A 2005 meta-analysis of allo-HCT in patients with AML in CR1 pooled data from 5 studies (total N=3100 patients). Among those patients, 1151 received allo-HCT, and 1949 were given alternative therapies including chemotherapy and autologous HCT. All studies employed natural randomization based on donor availability and intention-to-treat analysis, with OS and disease-free survival (DFS) as outcomes of interest. This analysis showed a significant advantage for allo-HCT in terms of OS for the entire cohort (fixed-effects model HR=1.17; 95% CI, 1.06 to 1.30; p=0.003; random-effects model HR=1.15; 95% CI, 1.01 to 1.32; p=0.037) even though none of the individual studies did so. Meta-regression analysis showed that the effect of allo-HCT on OS differed depending on the cytogenetic risk groups of patients, suggesting a significant benefit for poor-risk patients (HR=1.39, 95% CI not reported), indeterminate benefit for intermediate-risk
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cases, and no benefit in better-risk patients compared with alternative approaches. Reviewers cautioned that the compiled studies used different definitions of risk categories than other groups (e.g., Southwest Oncology Group [SWOG], Medical Research Council, European Organisation for Research and Treatment of Cancer, Gruppo Italiano Malattie Ematologiche dell’ Adulto), but examination showed cytogenetic categories in those definitions are very similar to recent guidelines from the NCCN. Although the statistical power of the meta-regression analysis was limited by small numbers of cases, the results of this meta-analysis are supported in general by data from other reviews.

Evidence from the meta-analysis suggests patients with better prognosis (as defined by cytogenetics) may not realize a significant survival benefit with allo-HCT in CR1 that outweighs the risk of associated morbidity and nonrelapse mortality. However, there is considerable genotypic heterogeneity within the 3 WHO cytogenetic prognostic groups that complicates generalization of clinical results based only on cytogenetics. For example, patients with better prognosis disease (e.g., core-binding factor AML) based on cytogenetics, and a variant in the c-KIT gene of leukemic blast cells, do just as poorly with postremission standard chemotherapy as patients with cytogenetically poor-risk AML. Similarly, patients with cytogenetically normal AML (intermediate prognosis disease) can be subcategorized into groups with better or worse prognosis based on the mutational status of the nucleophosmin gene (NPM1) and the FLT3 gene (the FLT3 gene, as defined in the Background/Overview section, is a gene that encodes FMS-like receptor tyrosine kinase 3, a growth factor active in hematopoiesis). Thus, patients with variants in NPM1 but without FLT3 internal tandem duplications have postremission outcomes with standard chemotherapy that are similar to those with better prognosis cytogenetics; in contrast, patients with any other combination of variants in those genes have outcomes similar to those with poor prognosis cytogenetics. These examples highlight the rapidly growing body of evidence for genetic variants as additional predictors of prognosis and differential disease response to different treatments. It follows that, because the earlier clinical trials compiled in the meta-analysis described here did not account for genotypic differences that affect prognosis and alter outcomes, it is difficult to use the primary trial results to draw conclusions on the role of allo-HCT in different patient risk groups.

A meta-analysis by Buckley et al (2017) evaluated the relation between minimal residual disease (MRD) at the time of HCT and posttransplantation outcomes. The literature search, conducted through June 2016, identified 19 studies (total N=1431 patients) for inclusion. Risk of bias was assessed using a modified version of Quality of Prognostic Studies instrument, which focused on: prognostic factor measurement, study confounding, and statistical analysis and reporting. Five studies were considered at high risk for bias, nine were at moderate risk, and five were at low risk. The following variables were collected from each study: age, follow-up, adverse-risk cytogenetics, conditioning type (myeloablative or reduced-intensity), MRD detection method, and survival. Reviewers reported that the presence of MRD at time of transplantation was associated with higher relapse and mortality. This association was seen regardless of patient age and type of conditioning, which suggests that an intense conditioning regimen may not be able to overcome the adverse impact of MRD.
Prospective Studies
A 2014 study compared outcomes of 185 matched pairs from a large multicenter trial (AMLCG99). Patients younger than 60 years of age who underwent allo-HCT in CR1 were matched to patients who received conventional postremission chemotherapy. The main matching criteria were AML type, cytogenetic risk group, patient age, and time in CR1. In the overall pairwise-compared AML population, the projected 7-year OS rate was 58% for the allo-HCT and 46% for the conventional postremission treatment group (p=0.037). Relapse-free survival was 52% in the allo-HCT group and 33% in the control group (p<0.001). OS was significantly longer for allo-HCT patient subgroups with nonfavorable chromosomal aberrations, patients older than 45 years, and patients with secondary AML or high-risk myelodysplastic syndrome. For the entire patient cohort, postremission therapy was an independent factor for OS (HR=0.66; 95% CI, 0.49 to 0.89 for allo-HCT vs conventional chemotherapy) among age, cytogenetics, and bone marrow blasts after the first induction cycle.

Section Summary: Allo-HCT for Chemotherapy-Responsive Consolidation
Evidence for the use of allo-HCT for patients with AML in CR1 consists RCTs and matched cohort studies. Some studies have compared allo-HCT with autologous HCT or with postremission chemotherapy. OS rates and DFS rates were favorable for allo-HCT compared with conventional chemotherapy. In a paired comparison with patients receiving chemotherapy, patients receiving allo-HCT experienced significantly higher relapse-free survival rates. Survival rates appear to be associated with presence of minimal residual disease and cytogenetic prognosis group.

ALLO-HCT FOR AML REFRACTORY TO CHEMOTHERAPY
Conventional dose induction chemotherapy will not produce remission in 20% to 40% of patients with AML, connoting refractory AML. An allo-HCT using a matched related donor or matched unrelated donor represents the only potentially curative option for these patients. In several retrospective studies, OS rates have ranged from 13% at 5 years to 30% at 3 years, although this procedure is accompanied by nonrelapse mortality rates of 25% to 62% in this setting. For patients who lack a suitable donor (matched related donor or matched unrelated donor), alternative treatments include salvage chemotherapy with high-dose cytarabine or etoposide-based regimens, monoclonal antibodies (e.g., gemtuzumab ozogamicin), multidrug resistance modulators, and other investigational agents (e.g., FLT3 antagonists). Because it is likely that stem cell preparations will be contaminated with malignant cells in patients whose disease is not in remission, upfront autologous HCT has no role in patients who fail induction therapy.

Section Summary: Allo-HCT for AML Refractory to Chemotherapy
Evidence for the use of allo-HCT for individuals with primary AML refractory to chemotherapy consists of retrospective studies compiled from data from phase 3 trials and registries. OS rate estimates are 13% at 5 years and 30% at 3 years; however, the procedure is accompanied by high rates of nonrelapse mortality (estimates range, 25%-62%). Nonetheless, these results may provide clinically meaningful benefit for such patients who do not have other treatment options. Autologous HCT is not recommended for patients who have failed induction therapy, because malignant cells may be included in the stem cell preparation process.
ALLOGENEIC OR AUTOLOGOUS HCT FOR RELAPSED AML AFTER CHEMOTHERAPY

Most patients with AML will experience disease relapse after attaining a CR1. Conventional chemotherapy is not curative in most patients following disease relapse, even if a second complete remission (CR2) can be achieved.

A 2005 study by Breems et al evaluated retrospective data from 667 patients who had relapsed, among a total of 1540 patients entered in 3 phase 3 trials who had received HCT during CR1. The analysis suggested that use of allo-HCT among relapsed patients can produce 5-year OS rates of 26% to 88%, depending on cytogenetic risk stratification. Because reinduction chemotherapy may be associated with substantial morbidity and mortality, patients whose disease has relapsed and who have a suitable donor may proceed directly to allo-HCT.

In patients without an allogeneic donor or who are not candidates for allo-HCT due to age or other factors, autologous HCT may achieve prolonged DFS in 9% to 55% of patients in CR2 depending on risk category. However, because it is likely that stem cell preparations will be contaminated with malignant cells in patients whose disease is not in remission, and it is often difficult to achieve CR2 in these patients, autologous HCT in this setting is usually limited to patients who have a sufficient stem cell preparation remaining from collection in CR1.

Allo-HCT is often performed as salvage therapy for patients who have relapsed after conventional chemotherapy or autologous HCT. The decision to attempt reinduction or proceed directly to allo-HCT is based on the availability of a suitable stem cell donor and the likelihood of achieving remission, the latter being a function of cytogenetic risk group, duration of CR1, and the patient’s health status. Registry data have shown DFS rates of 44% using sibling allografts and 30% with matched unrelated donor allografts at 5 years for patients transplanted in CR2, and DFS rates of 35% to 40% using sibling transplants and 10% with matched unrelated donor transplants for patients with induction failure or in relapse following HCT.

In a 2017 retrospective chart review, Frazer et al assessed characteristics that might predict OS, relapse rate, and nonrelapse mortality of HCT in patients with relapsed AML. Data were abstracted from 55 consecutive patients who underwent allo-HCT for AML in CR2. OS rates at 1, 3, and 5 years posttransplant were 60%, 45%, and 37%, respectively. None of the following pretransplant variables was significantly associated with OS, relapse rate, or nonrelapse mortality: duration of first remission, patient age, cytogenetic risk category, post myelodysplastic syndrome, conditioning regimen, or donor type. Limitations of the study were its small sample size and selection parameters that included transplantations conducted across 21 years.

Section Summary: Allogeneic or Autologous HCT for Relapsed AML After Chemotherapy

Evidence for the use of HCT for individuals with relapsed AML consists of retrospective chart reviews compiling data from phase 3 trials and registries. DFS rates ranged from 30% to 44% depending on source of transplantation cells, and OS rates ranged from 26% to 88% depending on risk stratification. Because reinduction chemotherapy may be associated with high morbidity and mortality, HCT may be considered.
REDUCED-INTENSITY CONDITIONING ALLO-HCT

A body of evidence is accruing from clinical studies that RIC with allo-HCT may be used for consolidation therapy in patients with AML.

Systematic Reviews

A 2016 systematic review and meta-analysis by Rashidi et al calculated OS and relapse-free survival for patients older than 60 years of age with AML who underwent RIC HCT. A literature search, conducted through September 2015, identified 13 studies (total N=749 patients) for inclusion. Pooled estimates for relapse-free survival at 6 months, 1 year, 2 years, and 3 years were 62% (95% CI, 54% to 69%), 47% (95% CI, 42% to 53%), 44% (95% CI, 33% to 55%), and 35% (95% CI, 26% to 45%), respectively. Pooled estimates for OS at 6 months, 1 year, 2 years, and 3 years were 73% (95% CI, 66% to 79%), 58% (95% CI, 50% to 65%), 45% (95% CI, 35% to 54%), and 38% (95% CI, 29% to 48%), respectively.

A 2014 meta-analysis compared RIC and MAC regimens for allo-HCT in patients with AML. The analysis included 23 clinical trials reported between 1990 and 2013, with approximately 15,000 adults. Eleven studies included AML and myelodysplastic syndrome, and 5 included AML only. A subanalysis from 13 trials in patients with AML or myelodysplastic syndrome revealed that OS was comparable in patients who received either reduced-intensity or myeloablative transplants, and the two-year or less and 2-year or greater OS rates were equivalent between the 2 groups. The 2- to 6-year PFS, nonrelapse mortality, and acute and chronic GVHD rates were reduced after RIC HCT, but relapse rate was increased. Similar outcomes were observed regardless of disease status at transplantation. Among the RIC HCT recipients, survival rates were superior if patients were in CR at transplantation.

Randomized Controlled Trials

A randomized comparative trial in matched patient groups compared the net health benefit of allo-HCT with RIC to MAC. In this study, patients (18-60 years) were randomized to 4 doses of RIC (n=99) at 2 gray of total body irradiation plus fludarabine 150 mg/m², or to 6 doses of standard conditioning (n=96) at 2 gray of total body irradiation plus cyclophosphamide 120 mg/kg. All patients received cyclosporine and methotrexate as prophylaxis against GVHD. The primary end point was the incidence of nonrelapse mortality analyzed in the intention-to-treat population. This unblinded trial was stopped early because of slow accrual of patients. The incidence of nonrelapse mortality did not differ between the RIC and standard conditioning groups (cumulative incidence at 3 years, 13% [95% CI, 6% to 21%] vs 18% [95% CI, 10% to 26%]; HR=0.62; 95% CI, 0.30 to 1.31, respectively). Relapse cumulative incidence at 3 years was 28% (95% CI, 19% to 38%) in the RIC group and 26% (95% CI, 17% to 36%; HR=1.10; 95% CI, 0.63 to 1.90) in the standard conditioning group. The DFS rates at 3 years were 58% (95% CI, 49% to 70%) in the RIC group and 56% (95% CI, 46% to 67%; HR=0.85; 95% CI, 0.55 to 1.32) in the standard conditioning group. The OS rates at 3 years were 61% (95% CI, 50% to 74%) in the RIC group and 58% (95% CI, 47% to 70%; HR=0.77; 95% CI, 0.48 to 1.25) in the standard conditioning group. No outcomes differed significantly between groups. Grade 3 or 4 oral mucositis was less common in the RIC group (50 patients) than in the standard conditioning group (73 patients); the frequency of other adverse events such as GVHD and increased concentrations of bilirubin and creatinine did not differ significantly between groups.
A phase 2 single-center, randomized toxicity study published in 2013 compared MAC and RIC in patients who received allo-HCT to treat AML. Adults 60 years of age or younger with AML were randomized (1:1) to treatment with RIC (n=18) or MAC (n=19) for allo-HCT. A maximum median mucositis grade of 1 was observed in the RIC group compared with grade 4 in the MAC group (p<0.001). Hemorrhagic cystitis occurred in 8 (42%) of the patients in the MAC group and none (0%) in the RIC group (p<0.001). Results of renal and hepatic tests did not differ significantly between the groups. RIC-treated patients had faster platelet engraftment (p<0.01) and required fewer erythrocyte and platelet transfusions (p<0.001) and less total parenteral nutrition than those treated with MAC (p<0.01). Cytomegalovirus infection was more common in the MAC group (14/19) than in the RIC group (6/18) (p=0.02). Donor chimerism was similar in the 2 groups for CD19 and CD33 but was delayed for CD3 in the RIC group. Five-year treatment-related morbidity was approximately 11% in both groups, and rates of relapse and survival did not differ significantly. Patients in the MAC group with intermediate cytogenetic AML had a 3-year survival rate of 73% compared with 90% among those in the RIC group.

Comparative Trials
In a 2016 comparative study by European Society for Blood and Marrow Transplantation (EBMT), long-term survival was evaluated among patients with AML who underwent allo-HCT with RIC or with MAC regimens. Data from 701 patients receiving MAC and 722 patients receiving RIC were analyzed. Survival, relapse, and GVHD rates are summarized in Table 1. In a multivariate analysis, the following factors predicted nonrelapse mortality: RIC, age older than 55 years, advanced disease, and female donor to male recipient. Factors predicting chronic GVHD (a surrogate outcome for quality of life) were: in vivo T-cell depletion, advanced disease, and peripheral blood cell transplantation.

Table 1. Comparison of RIC and MAC Regimens in Patients Undergoing Allo-HCT

<table>
<thead>
<tr>
<th>Outcomes at 10-Year Follow-Up</th>
<th>RIC (n=722) Rate (95% CI), %</th>
<th>MAC (n=701) Rate (95% CI), %</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonrelapse mortality</td>
<td>20 (17 to 24)</td>
<td>35 (31 to 39)</td>
<td>&lt;0.001</td>
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<tr>
<td>Relapse</td>
<td>48 (44 to 52)</td>
<td>34 (31 to 38)</td>
<td>&lt;0.001</td>
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<tr>
<td>Leukemia-free survival, overall</td>
<td>32 (28 to 35)</td>
<td>31 (27 to 35)</td>
<td>0.57</td>
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<tr>
<td>Age 50-55 y</td>
<td>40 (33 to 46)</td>
<td>36 (32 to 41)</td>
<td>0.32</td>
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<tr>
<td>Age &gt;55 y</td>
<td>20 (14 to 26)</td>
<td>28 (24 to 32)</td>
<td>0.02</td>
</tr>
<tr>
<td>Overall survival</td>
<td>35 (32 to 39)</td>
<td>33 (29 to 37)</td>
<td>0.57</td>
</tr>
<tr>
<td>GVHD-free, relapse-free survival</td>
<td>21 (18 to 24)</td>
<td>22 (18 to 25)</td>
<td>0.79</td>
</tr>
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</table>

In a comparative study by Bitan et al (2014), outcomes were compared for children with AML who underwent allo-HCT using RIC regimens or MAC regimens. A total of 180 patients were evaluated; 39 underwent RIC and 141 received MAC regimens. Univariate and multivariate analyses showed no significant differences in the rates of acute and chronic GVHD, leukemia-free survival, and OS between treatment groups. The 5-year probabilities of OS with RIC and MAC regimens were 45% and 48%, respectively (p=0.99). Moreover, relapse rates were similar for RIC (39%) and MAC regimens (39%);
Hematopoietic Cell Transplantation for Acute Myeloid Leukemia

Policy #  00049
Original Effective Date: 01/28/2002
Current Effective Date: 11/15/2017

p=0.95), and recipients of MAC regimens were not at a higher risk for transplant-related mortality (16%) than recipients of RIC regimens (16%; p=0.73).

Noncomparative Studies
In a 2015 phase 2 study by Devine et al, 114 patients ages 60 to 74 years with AML in CR1 were treated with RIC and allo-HCT. Patients were followed for 2 years. The primary end point was DFS, and secondary end points were nonrelapse mortality, GVHD, relapse, and OS. Two years posttransplantation, the following rates were recorded: DFS, 42% (95% CI, 33% to 52%); OS, 48% (95% CI, 39% to 58%); nonrelapse mortality, 15% (95% CI, 8% to 21%); grades 2, 3, or 4 acute GVHD, 10% (95% CI, 4% to 15%); grades 2, 3, or 4 chronic GVHD, 28% (95% CI, 19% to 36%); and cumulative incidence of relapse, 44% (95% CI, 35% to 53%).

Section Summary: Reduced-Intensity Conditioning Allo-HCT
Evidence for the use of RIC and allo-HCT to treat patients with AML consists of a meta-analysis, 2 RCTs, and numerous comparative and noncomparative studies. In general, compared with MAC, RIC has comparable survival estimates (leukemia-free, overall), though relapse rates appear higher among patients receiving RIC in some studies.

AUTOLOGOUS HCT FOR CHEMOTHERAPY-RESPONSIVE CONSOLIDATION

Systematic Reviews
A meta-analysis published in 2004 by Nathan et al compared survival outcomes for autologous HCT in CR1 with standard chemotherapy or no further treatment in AML patients ages 15 to 55 years. Two types of studies were eligible: (1) 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 (2) randomized trials that compared autologous HCT with chemotherapy in all patients. Among a total of 4058 patients included in 6 studies, 2989 (74%) achieved CR1; 1044 (26%) were randomized to HCT (n=524) or to chemotherapy (n=520). Of the 5 studies for which OS data were available, outcomes with autologous HCT were better in three, and outcomes with chemotherapy were better in two. None of the differences were statistically significant, nor was the pooled estimate (fixed-effects model survival probability ratio, 1.01; 95% CI, 0.89 to 1.15; p=0.86). In all 6 studies, DFS was numerically superior with autologous HCT compared with chemotherapy (or no further treatment), but only one reported a statistically significant DFS probability associated with autologous HCT. However, the pooled estimate for DFS showed a statistically significant probability in favor of autologous HCT at 48 months posttransplant (fixed-effects model survival probability ratio, 1.24; 95% CI, 1.06 to 1.44; p=0.006).

There are several reasons why this meta-analysis did not demonstrate a statistically significant OS advantage for autologous HCT compared with chemotherapy given the significant estimate for DFS benefit. First, the pooled data showed a 6.45% greater nonrelapse mortality rate in autologous HCT recipients compared with chemotherapy recipients. Second, 14% of chemotherapy recipients whose disease relapsed ultimately achieved a sustained CR2 after undergoing an allogeneic or autologous HCT. The intention-to-treat analysis in the studies, which included the latter cases in the chemotherapy group, may have
inappropriately inflated OS rates favoring chemotherapy. Furthermore, this analysis did not take into account the potential effects of cytogenetic or molecular genetic differences among patients that are known to affect response to treatment. Finally, the dataset comprised studies performed between 1984 and 1995, during which transplant protocols and patient management evolved significantly, particularly compared with current care.

A second meta-analysis, published in 2010 by Wang et al, evaluated autologous HCT plus further chemotherapy or no further treatment for patients with AML in CR1. Nine randomized trials involving 1104 adults who underwent autologous HCT and 1118 patients who received additional chemotherapy or no additional treatment were identified. Analyses suggested that autologous HCT in CR1 is associated with statistically significant reduction of relapse risk (RR=0.56; 95% CI, 0.44 to 0.71; p=0.001) and significant improvement in DFS (HR=0.89; 95% CI, 0.80 to 0.98), but at the cost of an increased nonrelapse mortality rate (RR=1.90; 95% CI, 1.34 to 2.70; p=0.23). There were more deaths during the first remission among patients assigned to autologous HCT than among the chemotherapy recipients or further untreated patients. As a consequence of the increased nonrelapse mortality rate, no statistical difference in OS (HR=1.05; 95% CI, 0.91 to 1.21) was associated with the use of autologous HCT, compared with further chemotherapy or no further therapy. These results are concordant with the earlier meta-analysis.

Randomized Controlled Trials
A prospective, randomized phase 3 trial by Vellenga et al (2011) compared autologous HCT plus intensive consolidation chemotherapy among patients (range, 16-60 years) with newly diagnosed AML of similar risk profiles in CR1. After 2 cycles of intensive chemotherapy (etoposide and mitoxantrone), patients in CR1—who were not candidates for allo-HCT—were randomized to a third consolidation cycle of the same chemotherapy (n=259) or autologous HCT (n=258). The HCT group experienced an upward trend toward superior relapse-free survival compared with the chemotherapy group at 5 years (38% vs 29%, respectively, p=0.065). HCT patients also had a lower relapse rate at 5 years (58%) compared with chemotherapy recipients (70%; p=0.02). OS did not differ between the HCT group (44%) and the chemotherapy group (41%; p=0.86). Nonrelapse mortality rates were higher in the autologous HCT group (4%) than in the chemotherapy consolidation group (1%; p=0.02). Despite this difference in nonrelapse mortality, the relative equality of OS rates was attributed by the investigators to a higher proportion of successful salvage treatments—second-line chemotherapy, autologous or allo-HCT—in the chemotherapy consolidation recipients that were not available to the autologous HCT patients. This large trial has shown an advantage for postremission autologous HCT in reducing relapse, but similar OS rates secondary to better salvage of chemotherapy-consolidated patients.

Section Summary: Autologous HCT for Chemotherapy-Responsive Consolidation
Evidence for the use of autologous HCT for patients with AML who do not have a suitable allogeneic donor or who cannot tolerate an allogeneic procedure consists of several RCTs comparing autologous HCT with chemotherapy and prospective cohort studies. Meta-analyses of these studies and trials reported improved DFS and relapse but did not find a significant improvement in OS. A potential explanation for this discrepancy between DFS and OS is the increased nonrelapse mortality rate experienced by patients in the transplantation group.
SUMMARY OF EVIDENCE
For individuals who have cytogenetic or molecular intermediate- or poor-risk AML in CR1 who receive allo-HCT with MAC, the evidence includes RCTs and matched cohort studies. Relevant outcomes are OS and disease-specific survival. The evidence has revealed that allo-HCT is better at improving overall and disease-specific survival rates in patients with AML in CR1 than conventional chemotherapy. All trials employed natural randomization based on donor availability and an intention-to-treat analysis. Survival rates appear to be associated with 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 3 trials and registry data. Relevant outcomes are OS and disease-specific survival. The evidence would suggest that allo-HCT improves overall and disease-specific survival rates in patients with refractory 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 clinically meaningful benefit for such 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 3 trials and registry data. Relevant outcomes are OS and disease-specific survival. 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 RIC, the evidence includes 2 RCTs and other comparative and noncomparative studies. Relevant outcomes are OS, disease-specific survival, and treatment-related morbidity. The RCTs compared RIC with MAC and reported similar rates in nonrelapse mortality, relapse, and OS though one of the trials was stopped prematurely due to a 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 is likely 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 or beyond without a suitable allo-HCT donor who receive 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. Relevant outcomes are OS and disease-specific survival. Compared with chemotherapy, patients undergoing autologous HCT experienced reduced relapse and improved DFS
rates. 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.

References

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Hematopoietic Cell Transplantation for Acute Myeloid Leukemia

Policy # 00049  
Original Effective Date: 01/28/2002  
Current Effective Date: 11/15/2017


Policy History

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<tr>
<th>Date</th>
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<td>12/06/2001</td>
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<td>01/28/2002</td>
<td>Managed Care Advisory Council approval</td>
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<td>03/31/2004</td>
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<td>04/20/2004</td>
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<td>07/07/2006</td>
<td>Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.</td>
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<td>08/02/2006</td>
<td>Medical Director Review</td>
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<td>08/09/2006</td>
<td>Medical Policy Committee approval, format revisions, addition of FDA/other governmental regulations, references updates. Coverage eligibility unchanged.</td>
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<td>07/22/2009</td>
<td>Medical Policy Committee approval. Extensive revision of coverage section. Updated background/overview, rationale and references.</td>
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<td>07/01/2010</td>
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<td>09/04/2014</td>
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<td>08/03/2015</td>
<td>Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.</td>
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<td>10/29/2015</td>
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<td>11/16/2015</td>
<td>Medical Policy Implementation Committee approval. Coverage statements clarified with new language.</td>
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Hematopoietic Cell Transplantation for Acute Myeloid Leukemia

Policy # 00049
Original Effective Date: 01/28/2002
Current Effective Date: 11/15/2017

11/03/2016 Medical Policy Committee review
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017 Medical Policy Committee review
11/15/2017 Medical Policy Implementation Committee approval. Removed "stem" from the policy title, coverage statements and text. Added the phrase 'but can be brought into CR with intensified induction chemotherapy to the last criteria bullet for HCT using a myeloablative conditioning regimen. Added Policy Guidelines section from Blue Cross Blue Shield Association.

Next Scheduled Review Date: 11/2018

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means

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Hematopoietic Cell Transplantation for Acute Myeloid Leukemia

Policy # 00049
Original Effective Date: 01/28/2002
Current Effective Date: 11/15/2017

of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
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A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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