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Hematopoietic Cell Transplantation for Acute Myeloid Leukemia

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Coverage

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 section for information on risk stratification); or
- AML that is refractory to standard induction chemotherapy but can be brought into complete remission (CR) with intensified induction chemotherapy; or
- AML that relapses following chemotherapy induced CR1 but can be brought into second complete remission (CR2) or beyond with intensified induction chemotherapy; or
- AML in individuals 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 individuals 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 section).

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

Allogeneic and autologous HCT **are considered experimental, investigational and/or unproven** in individuals not meeting any of the above criteria.

Policy Guidelines

Primary refractory acute myeloid leukemia (AML) is defined as leukemia that does not achieve a complete remission after conventionally dosed (nonmarrow ablative) chemotherapy.

In the French-American-British 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 (French-American-British classification M4 or M5).

The newer, currently preferred, World Health Organization 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 World Health Organization system was adapted by National Comprehensive Cancer Network to estimate individual prognosis to guide management, as shown in Table PG1.

Table PG1. Risk Status of Acute Myeloid Leukemia Based on Genetic Factors

Risk Category	Genetic Abnormality
Favorable	t(8;21) (q22;q22.1)/*RUNX1::RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11* Mutated *NPM1* without *FLT3*-ITD bZIP in-frame mutated *CEBPA*
Intermediate	Mutated *NPM1* with *FLT3*-ITD Wild-type *NPM1* without *FLT3*-ITD (without adverse-risk genetic

	lesions) t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A* Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Poor/Adverse	t(6;9)(p23;q34.1)/*DEK-NUP214* t(v;11q23.3)/*KMT2A*-rearranged t(9;22)(q34.1;q11.2)/*BCR::ABL1* t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2,MECOM(EVI1)* t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged -5 or del(5q); -7; -17/abn(17p) Complex karyotype, monosomal karyotype Wild-type *NPM1* and *FLT3*-ITD^{high} Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and ZRSR2* Mutated *TP53*

AML: acute myeloid leukemia; bZIP: basic leucine zipper; 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 (antigen-D related) 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 individual, for which there usually is sharing of only 3 of the 6 major histocompatibility antigens. Most individuals 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.

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). Hematopoietic cell transplantation refers to a procedure that infuses hematopoietic stem cells to restore bone marrow function in individuals with cancer who receive bone marrow-toxic doses of drugs with or without whole-body radiotherapy.

Acute Myeloid Leukemia Treatment

Complete remission of AML 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 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.

Hematopoietic Cell Transplantation

Hematopoietic cell transplantation 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). These cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allo-HCT, 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. Human leukocyte antigen 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 (GVHD), 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 GVHD.

Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation
Reduced-intensity conditioning (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 (MAC) 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 nonrelapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and nonrelapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. Reduced-intensity conditioning regimens range from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. In this policy, the term RIC will refer to all conditioning regimens intended to be nonmyeloablative.

A 2015 review in the *New England Journal of Medicine* summarized advances in the classification of AML, the genomics of AML and prognostic factors, and current and new treatments. (1) The National Comprehensive Cancer Network guidelines provide updated information on genetic markers for risk stratification, and additional recent reviews summarize information on novel therapies for AML. (2-4)

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.

Rationale

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Allogeneic Hematopoietic Stem Cell Transplant with Myeloablative Conditioning for Cytogenetic or Molecular Intermediate- or Poor-Risk Acute Myeloid Leukemia in Complete Remission

Clinical Context and Therapy Purpose

The purpose of allogeneic (allo-) hematopoietic cell transplantation (HCT) with myeloablative conditioning (MAC) in individuals who have cytogenetic or molecular intermediate- or poor-risk acute myeloid leukemia (AML) in first complete remission (CR1) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with cytogenetic or molecular intermediate- or poor-risk AML in CR1.

Interventions

The therapy being considered is allo-HCT with MAC. Allogeneic HCT with MAC is an option for post-remission or consolidation therapy in cytogenetic or molecular intermediate- or poor-risk AML. The purpose of post-remission therapy is to destroy undetectable leukemia cells remaining after induction chemotherapy.

Comparators

The following therapies are currently being used to make decisions about cytogenetic or molecular intermediate- or poor-risk AML in CR1: conventional chemotherapy.

Outcomes

The general outcomes of interest are survival outcomes (overall survival [OS], disease-specific survival [DSS], and disease-free survival [DFS]), relapse rates, and treatment-related morbidity. The median survival of individuals with AML varies with several known prognostic factors related to individual and tumor characteristics such as age, performance status, and karyotype. Overall, the median survival for individuals with AML without chemotherapy or HCT is less than

10 months; the median survival in individuals with chemotherapy but without HCT is approximately 20 months. (5) Individuals are followed up throughout their lifespan.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Masetti et al. (2022) conducted a meta-analysis of allo-HCT for pediatric patients with AML in CR1. (6) Both prospective and retrospective studies comparing allo-HCT to chemotherapy in higher-risk patients were considered. A total of 9 studies (5 prospective, 4 retrospective) were included; none of the prospective studies were randomized. The meta-analysis showed that OS was improved with allo-HCT compared with chemotherapy (risk ratio, 1.15; 95% confidence interval [CI], 1.06 to 1.24; I^2=0%). Similarly, DFS was improved with allo-HCT compared to chemotherapy (risk ratio, 1.31; 95% CI, 1.17 to 1.47; I^2=1%). Risk of relapse was higher among patients who received chemotherapy (risk ratio, 1.26; 95% CI, 1.07 to 1.49; I^2=23%).

A 2015 meta-analysis examined prospective trials of adults with intermediate-risk AML in CR1 who underwent HCT. (7) The analysis included 9 prospective, controlled studies that enrolled 1950 patients between the years 1987 and 2011 (sample range, 32 to 713 patients). In this meta-analysis, allo-HCT was associated with significantly better relapse-free survival (RFS), OS, and relapse rate than autologous HCT and/or chemotherapy (hazard ratio [HR], 0.68; 95% 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. (8) 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<.01); among intermediate-risk patients across 14 trials, the HR for OS was 0.83 (95% CI, 0.74 to 0.93; p<.01); and among good-risk patients across 16 trials, the HR for OS was 1.07 (95% CI, 0.83 to 1.38; p=.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 are in

line with those from another meta-analysis (9) 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 (N=3100 patients). (9) 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 DFS as outcomes of interest. This analysis showed a significant advantage for allo-HCT regarding OS for the entire cohort (fixed-effects model HR, 1.17; 95% CI, 1.06 to 1.30; p=.003; random-effects model HR, 1.15; 95% CI, 1.01 to 1.32; p=.037) even though none of the individual studies did so. Meta-regression analysis showed 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), an indeterminate benefit for intermediate-risk cases, and no benefit in better-risk patients compared with alternative approaches. Reviewers cautioned the compiled studies used different definitions of risk categories than other groups (e.g., SWOG, Medical Research Council, European Organisation for Research and Treatment of Cancer, Gruppo Italiano Malattie Ematologiche dell' Adulto). (10) 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. (11-14)

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 World Health Organization cytogenetic prognostic groups that complicates generalization of clinical results based only on cytogenetics. (15) For example, patients with better prognosis disease (e.g., core-binding factor AML) based on cytogenetics, and a variant in the *KIT* gene of leukemic blast cells, do just as poorly with post-remission standard chemotherapy as patients with cytogenetically poor-risk AML. (16) 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 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 post-remission 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. (17) 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 relationship between minimal residual disease (MRD) at the time of HCT and posttransplantation outcomes. (18) The literature search, conducted through June 2016, identified 19 studies (N=1431 patients) for inclusion. Risk of bias was assessed using a modified version of the 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, 9 were at moderate-risk, and 5 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 the 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

Bornhäuser et al. (2023) conducted an open-label, 2-arm, multicenter RCT in Germany to assess the ideal postremission strategy in intermediate-risk AML in CR1. (19) Adults with AML (age 18 to 60 years) in CR1 or CR with incomplete blood cell count recovery after conventional induction therapy who had availability of a human leukocyte antigen-matched sibling or unrelated donor were included and randomized 1:1 to receive allo-HCT or high-dose cytarabine (HiDAC) for consolidation and salvage HCT only in cases of relapse. The primary outcome was OS; DFS, incidence of relapse, treatment-related mortality, and quality of life measures according to the Medical Outcomes Study 36-Item Short-Form Health Survey were secondary outcomes. One hundred forty-three patients (mean age, 48.2 years, standard deviation, 9.8 years; 57% male) with AML were randomized. At 2 years, the probability of survival was 74% (95% CI, 62% to 83%) after primary allo-HCT and 84% (95% CI, 73% to 92%) after HiDAC (p=.22). Disease-free survival at 2 years was 69% (95% CI, 57% to 80%) after HCT compared with 40% (95% CI, 28% to 53%) after HiDAC (p=.001). The cumulative incidence of relapse at 2 years with allo-HCT was 20% (95% CI, 13% to 31%) compared with 58% (95% CI, 47% to 71%; p<.001) with HiDAC and nonrelapse mortality after allo-HCT was 9% (95% CI, 5% to 19%) versus 2% (95% CI, 0% to 11%) after HiDAC (p=.005). All 41 participants who relapsed after HiDAC proceeded to receive allo-HCT. There were no differences in quality of life measures between groups. Of note, this trial was closed earlier than anticipated due to slow patient accrual, which was a limitation. Additional limitations included the lack of stratification based on MRD and the use of a cytogenetic classifier at trial initiation (2012) which led to inclusion of some favorable-risk patients, which current guidelines would not recommend allo-HCT in CR1. In conclusion, primary allo-HCT during CR1 was not associated with superior OS compared to HiDAC in adults with intermediate-risk AML <60 years, although some secondary endpoints had promising results and were hypothesis generating.

A 2014 study compared outcomes of 185 matched pairs from a large multicenter trial (AMLCG99). (20) Patients younger than 60 years of age who underwent allo-HCT in CR1 were matched to patients who received conventional post-remission 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 allo-HCT and 46% for the conventional post-remission treatment group (p=.037). The RFS rate was 52% in the allo-HCT group and 33% in the control group (p<.001). The OS was significantly longer for allo-HCT patient subgroups with unfavorable chromosomal aberrations, patients older than 45 years, and patients with secondary AML or high-risk myelodysplastic syndrome.

For the entire patient cohort, post-remission 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.

Retrospective Studies

Heidrich et al. (2017) conducted retrospective analyses of subgroups from 2 prospective clinical trials, including 497 patients with intermediate-risk AML who did not present with *NPM1*, *CEBPA*, or *FLT3* internal tandem duplication variants. (21) During the initial analysis (donor vs. no-donor), RFS rates were better for patients who had an available sibling donor (n=83) than for those who lacked a matched sibling donor (49% vs. 26%; HR, 0.5; 95% CI, 0.3 to 0.9; p=.02). A similar improvement was seen for OS, although not statistically significant (p=.08). The authors also conducted a time-dependent multivariate analysis to account for the significantly longer time-from-CR1 observed in patients treated with allo-HCT (median, 115 days) compared with those treated with post-remission chemotherapy (median, 78 days; p<.001). Rates of OS after 5 years were superior for the group who received allo-HCT than for those receiving chemotherapy (OS, 66% vs. 46%, respectively; HR, 0.58; 95% CI, 0.37 to 0.9; p=.02), as were rates of RFS (5-year RFS, 55% vs. 31%; HR, 0.51; 95% CI, 0.34 to 0.76; p=.001). The investigators acknowledged that 38% of the group assigned to post-remission chemotherapy received allo-HCT following a relapse, which might have contributed to a crossover effect.

Section Summary: Allogeneic Hematopoietic Cell Transplant with Myeloablative Conditioning for Cytogenetic or Molecular Intermediate- or Poor-Risk Acute Myeloid Leukemia in Complete Remission

Evidence for the use of allo-HCT for patients with AML in CR1 consists of systematic reviews, RCTs, and matched cohort studies. Some studies have compared allo-HCT with autologous HCT or with post-remission chemotherapy. In some studies, the OS 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 RFS rates. However, in a more recent RCT, there was no difference in OS between allo-HCT and HiDAC, although there were many limitations associated with this study. Two retrospective studies analyzed subgroups of allo-HCT patients who did not present with several common genetic variants or who presented with hyperleukocytosis. Survival rates appear to be associated with the presence of MRD and cytogenetic prognosis groups.

Allogeneic Hematopoietic Cell Transplant with Myeloablative Conditioning for Acute Myeloid Leukemia Refractory to Standard Induction Chemotherapy

Clinical Context and Therapy Purpose

The purpose of allo-HCT with MAC in individuals who have AML refractory to standard induction chemotherapy is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population(s) of interest is individuals with AML refractory to standard induction chemotherapy.

Interventions
The therapy being considered is allo-HCT with MAC. Allogeneic HCT is an option for AML refractory to standard induction chemotherapy. The purpose is to destroy leukemia cells remaining after induction chemotherapy.

Comparators
The following therapies are currently being used to make decisions about AML refractory to standard induction chemotherapy: conventional chemotherapy.

Outcomes
The general outcomes of interest are survival outcomes (OS, DSS, and DFS), relapse rates, and treatment-related morbidity. The median survival of individuals with AML varies with several known prognostic factors related to individual and tumor characteristics such as age, performance status, and karyotype. Overall, the median survival for individuals with AML without chemotherapy or HCT is less than 10 months; the median survival in individuals with chemotherapy but without HCT is approximately 20 months. (5) Individuals are followed up throughout their lifespan.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Retrospective Studies
Conventional dose induction chemotherapy will not produce remission in 20% to 40% of patients with AML, connoting refractory AML. (10) 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 30% at 3 years to 13% at 5 years, although this procedure is accompanied by nonrelapse mortality rates of 25% to 62% in this setting. (11) A 2022 observational study reported higher 3-year and 5-year OS (38% and 33%, respectively), but these rates may lack precision due to a small sample size (N=12). (22) Another small study reported 4-year OS of 51.0±10.6% among 29 patients who received allo-HCT and 46.2±9.0% among 34 patients who received salvage chemotherapy followed by allo-HCT, both for refractory AML. (23) 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. (24)

Section Summary: Allogeneic Hematopoietic Cell Transplant with Myeloablative Conditioning for Acute Myeloid Leukemia Refractory to Standard Induction 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. The OS rate estimates range from 30% to 38% at 3 years and 13% to 51% at 4 to 5 years; however, the procedure is accompanied by high rates of nonrelapse mortality (estimated range, 25% to 62%). Nonetheless, these results may provide a 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 Hematopoietic Cell Transplant with Myeloablative Conditioning for Relapsed Acute Myeloid Leukemia After Chemotherapy-Induced Remission

Clinical Context and Therapy Purpose

The purpose of allogeneic or autologous HCT with MAC in individuals who have relapsed AML after standard induction chemotherapy-induced CR1 is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population(s) of interest is individuals with AML who relapsed after standard induction chemotherapy-induced CR1.

Interventions

The therapy being considered is allo-HCT or autologous HCT. Allogeneic or autologous HCT are options for treatment of relapsed AML after chemotherapy-induced remission. The purpose of HCT is to destroy leukemia cells associated with recurrent AML.

Comparators

The following therapies are currently being used to make decisions about relapsed AML after chemotherapy-induced remission: conventional chemotherapy.

Outcomes

The general outcomes of interest are survival outcomes (OS, DSS, and DFS), relapse rates, and treatment-related morbidity. The median survival of individuals with AML varies with several known prognostic factors related to individual and tumor characteristics such as age, performance status, and karyotype. Overall, the median survival for individuals with AML without chemotherapy or HCT is less than 10 months; the median survival in individuals with chemotherapy but without HCT is approximately 20 months. (5) Individuals are followed up throughout their lifespan.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Retrospective Studies

Most patients with AML will experience disease relapse after attaining a CR1. (10) Conventional chemotherapy is not curative in most patients following disease relapse, even if a second complete remission (CR2) can be achieved.

A study by Breems et al. (2005) 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. (25)

Allo-HCT is often performed as salvage therapy for patients who have relapsed after conventional chemotherapy or autologous HCT. (24) The decision to attempt reinduction 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. (24)

In a retrospective chart review, Frazer et al. (2017) assessed characteristics that might predict OS, relapse rate, and nonrelapse mortality of HCT in patients with relapsed AML. (26) Data were abstracted from 55 consecutive patients who underwent allo-HCT for AML in CR2. The OS rates at 1, 3, and 5 years posttransplant were 60%, 45%, and 37%, respectively. None of the following pretransplant variables were 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.

In patients in CR2 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. (24, 27) 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 the collection in CR1. (24)

Section Summary: Allogeneic or Autologous Hematopoietic Cell Transplant with Myeloablative Conditioning for Relapsed Acute Myeloid Leukemia After Chemotherapy-Induced Remission
Evidence on the use of HCT for individuals with relapsed AML includes retrospective chart reviews compiling data from phase 3 trials and registries. The DFS rates ranged from 30% to 44% depending on the 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.

Allogeneic Hematopoietic Cell Transplant With Reduced-Intensity Conditioning for Cytogenetic or Molecular Intermediate- or Poor-Risk Acute Myeloid Leukemia in Remission
Clinical Context and Therapy Purpose
The purpose of allo-HCT with reduced-intensity conditioning (RIC) in individuals who have cytogenetic or molecular intermediate- or poor-risk AML in CR1 who cannot tolerate MAC is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations
The relevant population(s) of interest is individuals with cytogenetic or molecular intermediate- or poor-risk AML in CR1 who cannot tolerate MAC.

Interventions
The therapy being considered is allo-HCT with RIC. Allogeneic HCT with RIC is an option for post-remission therapy for cytogenetic or molecular intermediate- or poor-risk AML. The purpose of post-remission therapy is to destroy undetectable leukemia cells remaining after induction chemotherapy.

Comparators
The following therapies are currently being used to make decisions about cytogenetic or molecular intermediate- or poor-risk AML in CR1: conventional chemotherapy and allo-HCT with MAC.

Outcomes
The general outcomes of interest are survival outcomes (OS, DSS, and DFS), relapse rates, and treatment-related morbidity. The median survival of individuals with AML varies with several known prognostic factors related to individual and tumor characteristics such as age, performance status, and karyotype. Overall, the median survival for individuals with AML without chemotherapy or HCT is less than 10 months; the median survival in individuals with chemotherapy but without HCT is approximately 20 months. (5) Individuals are followed up throughout their lifespan.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

A body of evidence is accruing from clinical studies that RIC with allo-HCT may be used for consolidation therapy in patients with AML. (28-39)

Systematic Reviews

Song et al. (2021) evaluated the efficacy of RIC followed by allo-HCT in patients with AML and myelodysplastic syndrome via a meta-analysis of 6 RCTs (N=1413). (40) The 6 RCTs compared RIC to MAC before first allo-HCT in patients with AML in complete remission or myelodysplastic syndrome. The primary endpoint was OS. Results revealed that OS was not significantly different between RIC and MAC (HR, 0.95; 95% CI, 0.64 to 1.4; p=.80). The cumulative incidence of relapse was also similar between the groups (HR, 1.18; 95% CI, 0.88 to 1.49; p=.28). Nonrelapse mortality was significantly improved with RIC as compared to total body irradiation/ busulfan-based MAC (HR, 0.53; 95% CI, 0.36 to 0.8; p=.002); however, treosulfan-based MAC significantly reduced nonrelapse mortality as compared to RIC (HR, 1.67; 95% CI, 1.02 to 2.72; p=.04). Reduced-intensity conditioning was associated with a trend of increasing graft failure (p=.06); however, graft failure in both arms was rare. The authors concluded that RIC is recommended as an adequate option of preparative treatment before allo-HCT for patients with AML in complete remission or myelodysplastic syndrome. Limitations of the meta-analysis included the small number of included clinical trials, significant heterogeneity between included studies for some outcomes, and lack of blinding in some studies.

A systematic review and meta-analysis by Rashidi et al. (2016) calculated OS and RFS for patients older than 60 years of age with AML who underwent RIC HCT. (41) A literature search, conducted through September 2015, identified 13 studies (N=749 patients) for inclusion. Pooled estimates for RFS 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 with MAC regimens for allo-HCT in patients with AML. (42) 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 RIC or MAC

transplants, and the 2-year or less and 2-year or greater OS rates were equivalent between both conditioning groups. The 2- to 6-year progression-free survival, nonrelapse mortality, and acute and chronic graft-versus-host disease (GVHD) rates were reduced after RIC HCT, but the 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 or with MAC. (43-45) In this phase 3 trial, patients (18 to 60 years) were randomized to 4 doses of RIC (n=99) at 2 gray of total body irradiation plus fludarabine 150 mg/m^2, 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 endpoint 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 and 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 (2013) compared MAC with RIC in patients who received allo-HCT to treat AML. (46) 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 ($p<.001$). Hemorrhagic cystitis occurred in 8 (42%) of the patients in the MAC group and none (0%) in the RIC group ($p<.01$). Results of renal and hepatic tests did not differ significantly between groups. The RIC-treated patients had faster platelet engraftment ($p<.01$) and required fewer erythrocyte and platelet transfusions ($p<.001$) and less total parenteral nutrition than those treated with MAC ($p<.01$). Cytomegalovirus infection was more common in the MAC group (14/19) than in the RIC group (6/18; $p=.02$). 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

Russell et al. (2022) published the results of an observational study of adults aged 60 to 70 years who underwent allo-HCT with RIC compared to patients who received only chemotherapy and did not undergo transplant. (47) A total of 932 patients with AML (not favorable risk) in remission were followed for 60 months, and 144 received allo-HCT with RIC. Five-year OS was 37% among transplant recipients. Allo-HCT with RIC led to improved OS compared to no transplant (37% vs. 20%, respectively; HR, 0.67; 95% CI, 0.53 to 0.84). Relapse-free survival was also improved with allo-HCT with RIC (32% vs. 13%, respectively).

In a 2016 comparative study by the European Society for Blood and Marrow Transplantation, long-term survival was evaluated among patients with AML who underwent allo-HCT with RIC or with MAC regimens. (48) 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 10-Year Outcomes for Reduced-Intensity Conditioning and Myeloablative Conditioning Regimens in Patients Undergoing Allogeneic Hematopoietic Cell Transplant

Outcomes	RIC (n=722) Rate (95% CI), %	MAC (n=701) Rate (95% CI), %	P
Nonrelapse mortality	20 (17 to 24)	35 (31 to 39)	<0.001
Relapse	48 (44 to 52)	34 (31 to 38)	<0.001
Leukemia-free survival, overall	32 (28 to 35)	31 (27 to 35)	0.57
Age 50-55 y	40 (33 to 46)	36 (32 to 41)	0.32
Age >55 y	20 (14 to 26)	28 (24 to 32)	0.02
Overall survival	35 (32 to 39)	33 (29 to 37)	0.57
GVHD-free, relapse-free survival	21 (18 to 24)	22 (18 to 25)	0.79

Adapted from Shimoni et al. (2016). (48)
CI: confidence interval; GVHD: graft-versus-host disease; MAC: myeloablative conditioning; RIC: reduced-intensity conditioning; y: year(s).

In a comparative study by Bitan et al. (2014), outcomes were compared for children with AML who underwent allo-HCT using RIC or MAC regimens. (49) 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=.99). Moreover, relapse rates were similar for RIC (39%) and MAC regimens (39%; p=.95), and recipients of MAC regimens were not at a higher risk for transplant-related mortality (16%) than recipients of RIC regimens (16%; p=.73).

Noncomparative Studies

In a phase 2 study by Devine et al. (2015), 114 patients ages 60 to 74 years with AML in CR1 were treated with RIC and allo-HCT. (50) Patients were followed for 2 years. The primary endpoint was DFS, and secondary endpoints were nonrelapse mortality, GVHD, relapse, and OS. Two years after transplantation, 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: Allogeneic Hematopoietic Cell Transplant With Reduced-Intensity Conditioning for Cytogenetic or Molecular Intermediate- or Poor-Risk Acute Myeloid Leukemia in Remission

Evidence for the use of RIC and allo-HCT to treat patients with AML consists of 2 RCTs, 3 meta-analyses, 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 Hematopoietic Cell Transplant for Acute Myeloid Leukemia in Remission With Chemotherapy-Responsive Consolidation

Clinical Context and Therapy Purpose

The purpose of autologous HCT in individuals with AML in remission who do not have a suitable allo-HCT donor is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with AML in remission who do not have a suitable allo-HCT donor.

Interventions

The therapy being considered is autologous HCT. For individuals with AML in remission without an acceptable allo-HCT donor, autologous HCT is an option for consolidation therapy.

Comparators

The following therapies are currently being used to make decisions about the treatment of AML in remission when no suitable allo-HCT donor is available: conventional chemotherapy.

Outcomes

The general outcomes of interest are survival outcomes (OS, DSS, and DFS), relapse rates, and treatment-related morbidity. The median survival of individuals with AML varies with several known prognostic factors related to individual and tumor characteristics such as age, performance status, and karyotype. Overall, the median survival for individuals with AML without chemotherapy or HCT is less than 10 months; the median survival in individuals with

chemotherapy but without HCT is approximately 20 months. (5) Individuals are followed up throughout their lifespan.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

A meta-analysis published by Nathan et al. (2004) compared survival outcomes for autologous HCT in CR1 with standard chemotherapy or no further treatment in AML patients ages 15 to 55 years. (51) 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 3, and outcomes with chemotherapy were better in 2. 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=.86). In all 6 studies, DFS was numerically superior using autologous HCT compared with chemotherapy (or no further treatment), but only 1 reported a statistically significant DFS probability associated with autologous HCT. 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=.006). This review 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 by Wang et al. (2010), evaluated autologous HCT plus further chemotherapy or no further treatment for patients with AML in CR1. (52) 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 a statistically significant reduction of relapse risk (relative risk, 0.56; 95% CI, 0.44 to 0.71; p=.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 (relative risk, 1.90; 95% CI, 1.34 to 2.70; p=.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

The RCTs published after the meta-analyses will be reviewed here.

A prospective, randomized phase 3 trial by Vellenga et al. (2011) compared autologous HCT with intensive consolidation chemotherapy among patients (range, 16 to 60 years) with newly diagnosed AML of similar risk profiles in CR1. (53) 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 RFS (38%) compared with the chemotherapy group at 5 years (29%; p=.065). The HCT patients also had a lower relapse rate at 5 years (58%) compared with chemotherapy recipients (70%; p=.02). The OS did not differ between the HCT group (44%) and the chemotherapy group (41%; p=.86). Nonrelapse mortality rates were higher in the autologous HCT group (4%) than in the chemotherapy consolidation group (1%; p=.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 post-remission autologous HCT in reducing relapse, but similar OS rates secondary to better salvage of chemotherapy-consolidated patients.

Miyamoto et al. (2018) reported results of a randomized, multicenter phase 3 trial conducted in 24 centers in Japan from 2003 to 2011 that compared autologous HCT versus HiDAC consolidation as post-remission therapy in AML. (54) This trial enrolled 240 patients between 15 and 64 years of age with newly diagnosed favorable- and intermediate-risk AML and Eastern Cooperative Oncology Group (ECOG) performance status of <3; 87 of those who achieved CR1 were randomized to autologous HCT or HiDAC. The study was powered to include 122 patients with 5 years of accrual and 3 years of post-accrual follow-up to detect a difference in DFS at 3 years of 40% versus 65%. Approximately one-third of the patients had favorable risk AML and the remaining two-thirds had intermediate-risk AML. The median age was 48 years. Median follow-up was approximately 4.5 to 5 years. Three-year DFS rate was 41% (95% CI, 27% to 55%) in the HiDAC group and 55% (95% CI, 38% to 68%) in the autologous HCT group (p=.25). Three-year OS was 77% (95% CI, 61% to 87%) versus 68% (95% CI, 52% to 80%) (p=.67). Cumulative incidence of relapse was 54% versus 41% (p=.22). There were no differences between the HiDAC and autologous HCT groups in the incidence of liver or renal dysfunction. The incidence of life-threatening infectious complications (p=.003) and mucositis/diarrhea (p=.002) was significantly higher in the autologous HCT group.

Section Summary: Autologous Hematopoietic Cell Transplant for Acute Myeloid Leukemia in Remission With 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 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 acute myeloid leukemia (AML) in first complete remission (CR1) who receive allogeneic (allo-) hematopoietic cell transplant (HCT) with myeloablative conditioning (MAC), the evidence includes systematic reviews, randomized controlled trials (RCTs), and matched cohort studies. Relevant outcomes are overall survival (OS) and disease-specific survival (DSS). The majority of the evidence has revealed that allo-HCT is better at improving OS and DSS rates in patients with AML in CR1 than conventional chemotherapy. One RCT found no difference in OS between allo-HCT and high-dose cytarabine, although the study had many limitations. 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 an 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 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 an 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 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 an 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 (RIC), the evidence includes 2 RCTs, 3 meta-analyses, and other comparative and noncomparative studies. Relevant outcomes are OS, DSS, and treatment-related morbidity. The RCTs compared RIC with MAC and reported similar rates in nonrelapse mortality, relapse, and OS, though 1 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 an 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 DSS. Compared with chemotherapy, patients undergoing autologous HCT experienced reduced relapse and improved disease-free survival (DFS) rates. The OS did not differ between the groups. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American Society for Transplantation and Cellular Therapy

In 2020, the American Society for Transplantation and Cellular Therapy published expert panel recommendations on the role of hematopoietic cell transplant (HCT) in newly-diagnosed adult acute myeloid leukemia (AML). (55) Recommendations were generated based on findings from a systematic review and graded based on prespecified criteria. Expert panel recommendations regarding allogeneic HCT (allo-HCT) and autologous HCT and the grades of the recommendations are as follows:

- Patients with unfavorable-risk in first remission (CR1) should undergo allo-HCT. (Grade A)
- Patients with intermediate-risk in CR1 should undergo allo-HCT. (Grade B)
- Patients with favorable-risk in CR1 should not undergo allo-HCT. (Grade C)
- The role of secondary mutational abnormalities in selecting a patient for allo-HCT is unclear. (Grade N/A [not applicable])
- The presence of measurable residual disease at the end of induction therapy should be considered an indication to offer allo-HCT. (Grade C)
- The role of allo-HCT is unclear in patients with induction failure. (Grade N/A)
- Patients with secondary acute myeloid leukemia in CR1 should undergo allo-HCT. (Grade D)
- Patients with therapy-related acute myeloid leukemia in CR1 should undergo allo-HCT. (Grade D)
- Patients ≥ 60 years in CR1 should undergo allo-HCT. (Grade B)
- Autologous HCT is a good alternative to chemotherapy consolidation in patients who are not eligible for allo-HCT. (Grade B)
- Myeloablative conditioning should be the preferred type of conditioning in patients who are fit for myeloablative conditioning, but reduced-intensity conditioning is an acceptable alternative in unfit patients. (Grade D)

In 2015, the American Society for Transplantation and Cellular Therapy (formerly The American Society for Blood and Marrow Transplantation) published guidelines on indications for

autologous HCT and allo-HCT. (56) An updated guideline was published in 2020. (57) Table 2 summarizes recommendations for HCT in AML from the most recent guideline iteration.

Table 2. Recommendations for the Use of Hematopoietic Cell Transplantation to Treat Acute Myeloid Leukemia

Indication	Allo-HCT[a]	Autologous HCT[a]
AML, age <18 years		
First CR, low risk	N	N
First CR, intermediate risk	C	N
First CR, high risk	S	N
Second or greater CR	S	N
Not in remission	S	N
AML, age ≥18 years		
First CR, low risk	N	C
First CR, intermediate risk	S	C
First CR, high risk	S	N
Second CR	S	C
Third or greater CR	S	N
Not in remission	S	N

[a] Recommendations were classified as follows: S, standard of care (well-defined and generally supported by evidence in the form of high-quality clinical trials and/or observational studies); C, standard of care, clinical evidence available (large clinical trials are not available; however, sufficiently large cohort studies have shown efficacy with acceptable risk of morbidity and mortality); N, not generally recommended.
allo-HCT: allogeneic hematopoietic cell transplantation; AML: acute myeloid leukemia; CR: complete remission; HCT: hematopoietic cell transplantation

In 2022, the American Society of Transplantation and Cellular Therapy published guidance on the role of HCT in pediatric AML and myelodysplastic syndrome. (58) The guidelines state that HCT is recommended for patients in CR1 with unfavorable mutations/cytomolecular abnormalities but not for patients with favorable-risk lesions. HCT should also be considered for patients with primary induction failure, refractory disease after 2 to 3 cycles of chemotherapy, and relapse.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) clinical guideline (v.2.2026) (2) for AML frequently refers readers to the NCCN Guidelines for Hematopoietic Cell Transplantation. HCT is noted as a treatment option in several algorithms, including “Acute Myeloid Leukemia (Age ≥18 years).” Specific NCCN recommendations can be found at <https://www.nccn.org>.

Medicare National Coverage

The Centers for Medicare & Medicaid Services have the following national coverage determination on the use of cell transplantation for AML (59):

- Allogeneic: "...for the treatment of leukemia, leukemia in remission..."

- Autologous: "Acute leukemia in remission who have a high probability of relapse and who have no human leukocyte antigens (HLA)-matched."

Ongoing and Unpublished Clinical Trials

No clinical trials that would influence this policy were found as of November 2024.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	36511, 38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38220, 38221, 38222, 38230, 38232, 38240, 38241, 38242, 38243, 81265, 81266, 81267, 81268, 81370, 81371, 81372, 81373, 81374, 81375, 81376, 81377, 81378, 81379, 81380, 81381, 81382, 81383, 86805, 86806, 86807, 86808, 86812, 86813, 86816, 86817, 86821, 86822, 86825, 86826, 86828, 86829, 86830, 86831, 86832, 86833, 86834, 86835, 86849, 86950, 86985, 88240, 88241
HCPCS Codes	S2140, S2142, S2150

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
11/15/2025	Document updated. Coverage unchanged. No new references added; one updated.
04/01/2025	Reviewed. No changes.
02/01/2025	Document updated with literature review. Coverage unchanged. Added references 19 and 57; others updated.
01/01/2024	Document updated with literature review. Coverage unchanged. References 6, 21, 22, 39, 46, 56, and 57 added; others updated.
04/15/2022	Reviewed. No changes.
05/15/2021	Document updated with literature review. Coverage unchanged. Added references: 2-4 and 49-50, others removed.
09/01/2020	Reviewed. No changes.
07/15/2019	Document updated with literature review. Coverage statement regarding medical necessity for autologous hematopoietic cell transplantation modified to clarify that it applies to patients that are not candidates for allogeneic hematopoietic cell transplantation. Title changed from "Hematopoietic Stem-Cell Transplantation for Acute Myelogenous Leukemia (AML)." Added references: 1, 3, 17, 46, and 48.
04/15/2018	Reviewed. No changes.
12/01/2017	Document updated with literature review. Coverage unchanged.
06/01/2016	Reviewed. No changes.
11/15/2015	Document updated with literature review. The following was added: 1) This wording was added to the acute myelogenous leukemia (AML) that is refractory to standard induction chemotherapy criterion - "but can be brought into complete remission (CR) with intensified induction chemotherapy"; 2) This wording was added to individual medically necessary

	criterion as it had been previously considered experimental, investigational and/or unproven - “AML that relapses following chemotherapy-induced first CR but can be brought into second complete remission or beyond with intensified induction chemotherapy”; 3) This wording was added to AML in patients who have relapsed following a prior autologous HSCT criterion - “but can be brought into CR with intensified induction chemotherapy”; and 4) This coverage statement was added – “For conditions not listed above, allogeneic or autologous hematopoietic stem-cell transplantation is considered experimental, investigational and/or unproven”. Title changed from Stem-Cell Transplant for Acute Myelogenous Leukemia.
06/01/2014	Document updated with literature review. The following was changed: 1) expanded coverage to consider Allogeneic stem-cell support (AlloSCS) may be medically necessary for • poor- to intermediate-risk AML in remission, • AML that is refractory to, or relapses following, standard induction chemotherapy, or • AML in patients who have relapsed following a prior autologous stem-cell support (AuSCS) and are medically able to tolerate the procedure; 2) expanded coverage to consider AlloSCS may be medically necessary when reduced conditioning is used as a treatment of AML in patients who are in complete marrow and extramedullary remission, and who for medical reasons would be unable to tolerate a myeloablative conditioning regimen; 3) expanded coverage to consider: a) donor leukocyte infusion (DLI) and hematopoietic progenitor cell (HPC) boost as medically necessary for AML that has relapsed or is refractory following an AlloSCS procedure, to prevent relapse in the setting of a high-risk relapse, or to convert a patient from mixed to full chimerism; b) DLI and HPC boost are considered experimental, investigational and/or unproven following an AlloSCS treatment for AML that was originally considered experimental, investigational and/or unproven for the treatment of AML; and 4) expanded coverage to consider a) short tandem repeat (STR) markers medically necessary when used in pre- or post-stem-cell support testing of the donor and recipient DNA profiles as a way to assess the status of donor cell engraftment following AlloSCS for AML; b) all other uses of STR markers experimental, investigational and/or unproven, if not listed in the coverage section. Description and Rationale substantially revised.
04/01/2010	New medical document originating from: SUR703.017, Peripheral/Bone Marrow Stem-cell Transplantation (PSCT/BMT) for Non-Malignancies; SUR703.018, Peripheral/Bone Marrow Stem-cell Transplantation (PSCT/BMT) for Malignancies; SUR703.022, Cord Blood as a Source of Stem-cells (CBSC); SUR703.023, Donor Leukocyte Infusion (DLI); and SUR703.024, Tandem/Triple High-Dose Chemoradiotherapy with Stem-cell Support for Malignancies. Stem-cell transplant continues to be medically necessary when stated criteria are met. [NOTE: A link to the medical policies with the following titles can be found at the end of the medical policy SUR703.002,

	Stem-Cell Reinfusion or Transplantation Following Chemotherapy (General Donor and Recipient Information): • Peripheral/Bone Marrow Stem-cell Transplantation (PSCT/BMT) for Non-Malignancies; • Peripheral/Bone Marrow Stem-cell Transplantation (PSCT/BMT) for Malignancies; • Cord Blood as a Source of Stem-cells; • Donor Leukocyte Infusion (DLI); and • Tandem/Triple High-Dose Chemoradiotherapy with Stem-cell Support for Malignancies.