Kansas City

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Hematopoietic Stem-Cell Transplantation for Acute Myeloid Leukemia

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Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage hematopoietic stem-cell transplantation for acute myeloid leukemia when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

Autologous HSCT may be considered **medically necessary** to treat AML in first or second remission or relapsed AML if responsive to intensified induction chemotherapy.

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

- poor- to intermediate-risk AML in remission (see Considerations for information on risk stratification), or
- AML that is refractory to, or relapses following, standard induction chemotherapy, or
- AML in patients who have relapsed following a prior autologous HSCT and are medically able to tolerate the procedure.

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

When Policy Topic is not covered

Hematopoietic stem-cell transplantation for acute myeloid leukemia is not covered if the criteria are not met.

Considerations

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

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

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

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

The newer, currently preferred, World Health Organization (WHO) classification of AML incorporates and interrelates morphology, cytogenetics, molecular genetics, and immunologic markers in an attempt to construct a classification that is universally applicable and prognostically valid. The WHO system was adapted by the National Comprehensive Cancer Network (NCCN) to estimate individual patient prognosis to guide management, as shown in the following table:

Risk Status of AML Based on Cytogenetic and Molecular Factors

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

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

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for reduced-intensity conditioning (RIC) allogeneic HSCT. It is important to recognize that the myeloablative intensity of different conditioning regimens varies substantially and that the distinction between myeloablative regimens and RIC regimens has not been defined.2 In this setting, patient selection is critical, and variations exist in the criteria used by transplant centers in the United States and worldwide. In general, candidates for RIC or nonmyeloablative conditioning regimen allogeneic HSCT include patients whose age (typically >60 years) or comorbidities (eg, liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen. A patient whose disease relapses following a conventional myeloablative allogeneic HSCT could undergo a second myeloablative procedure if a suitable donor is available and the patient's medical status would permit it. However, this type of patient would likely undergo RIC prior to a second allogeneic HSCT if a complete remission could be re-induced with chemotherapy.

Autologous HSCT is used for consolidation treatment of intermediate- to poor-risk disease in complete remission, among patients for whom a suitable donor is not available. Better-risk AML often responds well to chemotherapy with prolonged remission if not cure.

The ideal allogeneic donors are HLA-identical siblings, matched at the HLA-A, B, and DR loci (6 of 6). Related donors mismatched at one locus are also considered suitable donors. A matched, unrelated donor identified through the National Marrow Donor Registry is typically the next option considered. Recently, there has been interest in haploidentical donors, typically a parent or a child of the patient, where usually there is sharing of only 3 of the 6 major histocompatibility antigens. The majority of patients will have such a donor; however, the risk of GVHD and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

Reimbursement for Stem Cell collection and storage are considered payable under the Transplant Benefit when billed as a one-time, all-inclusive charge.

Transplant Benefit

The date on which the Transplant Benefit starts accumulating is determined by the transplant coordinator. The Transplant Benefit ends when the Transplant Lifetime Maximum benefit (if applicable) has been exhausted.

Benefits include:

- hospitalization of the recipient for medically recognized transplants from a donor to a transplant recipient;
- evaluation tests requiring hospitalization to determine the suitability of both potential (member's benefits must be verified with regard to the potential donor who does not turn out to be the actual donor) and actual donors, when such tests cannot be safely and effectively performed on an outpatient basis (**Note:** The member's benefits must be verified with regard to the **potential** donor who does not turn out to be the **actual** donor.);
- hospital room, board and general nursing in semi-private rooms;
- special care units, such as coronary and intensive care;
- hospital ancillary services;
- physicians' services for surgery, technical assistance, administration of anesthetics, and medical care;
- acquisition, preparation, transportation, and storage of organ / tissue / cells;
- diagnostic services;
- drugs which require a prescription by federal law;
- medical and surgical care of the donor (related to the procurement of the organ / tissue / cells) if coverage is not available to the donor from any other source. (Covered services provided to a donor will be applied against the recipient's transplant maximum benefit, if applicable)

If the donor and recipient are both listed on the same (family) policy, BCBSKC charges only one deductible and one coinsurance, if applicable.

In addition to the specific organ criteria, transplant candidates must also meet the following general criteria, including, but not limited to:

- Since compliance is a major factor in transplant graft survival, the patient (or legal guardian) must have the ability to accept and understand the transplant procedure and to maintain compliance with long-term medical management and immunosuppression.
- If applicable, patients with a history of malignancy must have passed the recommended length of time to be considered cured for that specific cancer. A complete metastatic evaluation must be performed before a patient will be considered an acceptable transplant candidate.
- Patients with a history of alcohol or substance abuse must have a six month history of abstinence as evidenced by negative urine or serum drug screens taken randomly.
- The patient must have adequate cardiopulmonary status.
- The patient must be free from active infection.

A covered person is eligible for retransplantation as deemed medically necessary and appropriate by BCBSKC. Review of a retransplantation request will include review of the covered person’s compliance with relevant transplant selection criteria including, but not limited to, adherence to medication regimens, follow-up examinations and abstinence from the use of alcohol and drugs.

Coverage will **not** be provided for:

- Transplant services when the cost is covered by government, foundation or charitable grants
- The purchase price of organs which are sold rather than donated to the recipient.
- an artificial organ

Clinical trials for conditions other than those allowed in this policy may be available in the research setting. However, these trials are considered investigational and/or experimental and therefore contract exclusions.

Note: There are some state mandates in place that require insurance carriers to cover certain clinical trials under very specific guidelines. Please contact your BCBSKC representative for more information.

Description of Procedure or Service

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

A substantial body of published evidence supports the use of allogeneic HSCT as consolidation treatment for AML patients in first complete remission (CR1) who have intermediate- or high-risk disease and a suitable donor; this procedure is not indicated for patients in CR1 with good-risk AML.

Data also support the use of allogeneic HSCT for patients in second complete remission (CR2) and beyond who are in chemotherapy-induced remission and for whom a donor is available. Allogeneic HSCT is a consolidation option for those with primary refractory or relapsed disease who can be brought into remission once more with intensified chemotherapy and who have a donor. For patients who are in remission but don't have a suitable donor, evidence supports the use of autologous HSCT in consolidation; this procedure is not an option for those who are not in remission.

Allogeneic HSCT using reduced-intensity conditioning (RIC) is supported by evidence for use in patients who otherwise would be candidates for an allogeneic transplant, but who have comorbidities that preclude use of a myeloablative procedure. These conclusions were generally affirmed in a recent systematic review and analysis of published international guidelines and recommendations, including those of the European Group for Blood and Marrow Transplantation (EBMT), the American Society for Blood and Marrow Transplantation (ASBMT), the British Committee for Standards in Hematology (BCSH), the National Comprehensive Cancer Network, (NCCN), and the specific databases of the National Guideline Clearinghouse and the Guideline International Network database.

Background

Hematopoietic Stem-Cell Transplantation

Hematopoietic stem cells may be obtained from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD). Cord blood is discussed in greater detail in a separate policy.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing human leukocyte antigens (HLA) 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.

Conventional Preparative Conditioning for HSCT

The conventional ("classical") practice of allogeneic HSCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that develops after engraftment of allogeneic stem cells within the patient's bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in

any allogeneic HSCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HSCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient prior to undergoing bone marrow ablation. As a consequence, autologous HSCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

Reduced-Intensity Conditioning for Allogeneic HSCT

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden, but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HSCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For the purposes of this policy, the term "reduced-intensity conditioning" will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

Acute myeloid leukemia (sometimes called "acute nonlymphocytic leukemia" [ANLL]) 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. About 13,000 new cases are diagnosed annually.

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

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 (MDS); 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;aq12), or translocations or structural abnormalities involving 11q23. Younger patients may exhibit t(8;21) and inv(16) or t(16;16). AML patients with 11q23 translocations include two subgroups: AML in infants and therapy-related leukemia. Multilineage dysplasia AML must exhibit dysplasia in 50% or more of the cells of two lineages or more. It is associated with cytogenetic findings that include-7/del(7q), -5/del(5q), +8, +9, +11, del(11q), del(12p), -18, +19, del(20q)+21, and other translocations. AML not otherwise categorized includes disease that does not fulfill criteria for the other groups, and essentially reflects the morphologic and cytochemical features and maturation level criteria used in the FAB classification, except for the definition of AML as having a minimum 20% (as opposed to 30%)

blasts in the marrow. AML of ambiguous lineage is diagnosed when blasts lack sufficient lineage-specific antigen expression to classify as myeloid or lymphoid.

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

Complete remissions can be achieved initially using combination chemotherapy in up to 80% of AML patients. However, the high incidence of relapse has prompted research into a variety of post-remission strategies using either allogeneic or autologous HSCT.

Rationale

This policy was originally created in 1999 and has been regularly updated with searches of the MEDLINE database. The most recent MEDLINE search was performed through June 18, 2014. Hematopoietic stem-cell transplantation (HSCT) has been investigated as consolidation therapy for patients whose disease enters complete remission following initial induction treatment or as salvage therapy in patients who experience disease relapse or have disease that is refractory to induction chemotherapy.

Consolidation Therapy in Remission

Allogeneic HSCT

A meta-analysis of allogeneic HSCT in patients with acute myeloid leukemia (AML) in first complete remission (CR1) pooled data from 5 studies that included a total of 3,100 patients. [3] Among those patients, 1,151 received allogeneic HSCT and 1,949 were given alternative therapies including chemotherapy and autologous HSCT. All of the studies employed natural randomization based on donor availability, and an intention-to-treat analysis, with overall survival (OS) and disease-free survival (DFS) as outcomes of interest. This analysis showed a significant advantage of allogeneic HSCT in terms of OS for the entire cohort (fixed-effects model hazard ratio [HR]: 1.17; 95% confidence interval [CI]: 1.06-1.30; p=0.003; random-effects model HR: 1.15, 95% CI: 1.01–1.32; p=0.037) even though none of the individual studies did so. Meta-regression analysis showed that the effect of allogeneic HSCT on OS differed depending on the cytogenetic risk groups of patients, suggesting significant benefit for poor-risk patients (HR: 1.39, 95% CI not reported), indeterminate benefit for intermediate-risk cases, and no benefit in better-risk patients compared to alternative approaches. The authors caution that the compiled studies used different definitions of risk categories (e.g., SWOG, MRC, EORTC/GIMEMA), but examination shows cytogenetic categories in those definitions are very similar to the recent guidelines from the National Comprehensive Cancer Network (NCCN) outlined in the Policy Guidelines. [4] Furthermore, the statistical power of the meta-regression analysis is limited by small numbers of cases. However, the results of this meta-analysis are supported in general by data compiled in other reviews. [5-8]

Evidence from the meta-analysis cited here suggests patients with cytogenetically defined better-prognosis disease may not realize a significant survival benefit with allogeneic HSCT in CR1 that outweighs the risk of associated morbidity and non-relapse mortality (NRM). However, there is considerable genotypic heterogeneity within the 3 World Health Organization (WHO) cytogenetic prognostic groups that complicates generalization of clinical results based only on cytogenetics.
9 For example, patients with better-prognosis disease (for example, core-binding factor AML) based on cytogenetics, and a mutation in the c-kit gene of leukemic blast cells, do just as poorly with post-

remission standard chemotherapy as patients with cytogenetically poor-risk AML. 10 Similarly, individuals 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 (defined above in the policy Description). Thus, patients with mutations in *NPM1* but without *FLT3*-ITD (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 mutations in those genes have outcomes similar to those with poor-prognosis cytogenetics. 11 These examples highlight the rapidly growing body of evidence for genetic mutations 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 concerning the role of allogeneic HSCT in different patient risk groups.

A second meta-analysis has been published that incorporated data from 24 trials involving a total of 6,007 patients who underwent allogeneic HSCT in first complete remission [CR1]. 12 Among the total, 3,638 patients were stratified and analyzed according to cytogenetic risk (547 good-, 2,499 intermediate-, 592 poor-risk AML, respectively) using a fixed-effects model. Compared with either autologous HSCT or additional consolidation chemotherapy, the HR for OS among poor-risk patients across 14 trials was 0.73 (95% CI: 0.59–0.90; p<0.01); among intermediate-risk patients across 14 trials, the HR for OS was 0.83 (95% CI: 0.74–0.93; p<0.01); among good-risk patients across 16 trials, the HR for OS was 1.07 (95% CI: 0.83–1.38; 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 the previously cited meta-analysis 3 and the current Policy Statements for use of allogeneic HSCT as consolidation therapy for AML.

A recent study compared the outcome of 185 matched pairs of patients from a large multicenter clinical trial (AMLCG99).13 Patients younger than 60 years who underwent allogeneic HSCT 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 first CR. In the overall pairwise compared AML population, the projected 7-year overall survival (OS) rate was 58% for the allogeneic HSCT and 46% for the conventional postremission treatment group (p= 037; log-rank test). Relapse-free survival was 52% in the allogeneic HSCT group compared with 33% in the control group (p<0.001). Overall survival was significantly better for allogeneic HSCT in patient subgroups with non-favorable 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 (hazard ratio, 0.66; 95% CI, 0.49 to 0.89 for allogeneic HSCT versus conventional chemotherapy), among age, cytogenetics, and bone marrow blasts after the first induction cycle.

Autologous HSCT

A meta-analysis published in 2004 examined survival outcomes of autologous HSCT in CR1 versus standard chemotherapy or no further treatment in AML patients aged 15–55 years. 14 Two types of studies were eligible: 1) prospective cohort studies in which patients with an available sibling donor were offered allogeneic HSCT (biologic randomization) with random assignment of all others to autologous HSCT or chemotherapy (or no further treatment); and 2) randomized trials that compared autologous HSCT with chemotherapy in all patients. Among a total of 4058 patients included in 6 studies, 2989 (74%) achieved CR1; 1,044 (26%) were randomly allocated to HSCT (n=524) or chemotherapy (n=520). Of the 5 studies for which OS data were available, outcomes with autologous HSCT were better in 3, and outcomes with chemotherapy were better in 2. None of the differences reached statistical significance, nor did the pooled estimate reach statistical significance (fixed-effects model survival probability ratio=1.01; 95% CI: 0.89-1.15, p=0.86). In all 6 studies, DFS was numerically superior with autologous HSCT compared to chemotherapy (or no further treatment), but only 1 reported a statistically significant DFS probability associated with autologous HSCT. However, the pooled estimate for DFS showed a statistically significant probability in favor of autologous HSCT at 48

months post-transplant (fixed-effects model survival probability ratio=1.24, 95% CI: 1.06-1.44, p=0.006).

There are several possible reasons this meta-analysis did not demonstrate a statistically significant OS advantage for autologous HSCT compared to chemotherapy given the significant estimate for DFS benefit. First, the pooled data showed a 6.45% greater NRM rate in autologous HSCT recipients compared to chemotherapy recipients. Second, 14% of chemotherapy recipients whose disease relapsed ultimately achieved a sustained second remission after undergoing an allogeneic or autologous HSCT. The intent-to-treat analysis in the studies, which included the latter cases in the chemotherapy group, may have inappropriately inflated overall survival rates favoring chemotherapy. Furthermore, this analysis did not take into account 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 to current care.

A second meta-analysis published in 2010 evaluated autologous HSCT versus further chemotherapy or no further treatment for AML in CR1. [15] A total of 9 randomized trials involving 1,104 adults who underwent autologous HSCT and 1,118 who received additional chemotherapy or no additional treatment were identified. The analyses suggest that autologous HSCT in CR1 was associated with statistically significant reduction of relapse risk (relative risk [RR]: 0.56, 95% CI: 0.44, 0.71, p=0.0004) and significant improvement in DFS (HR: 0.89, 95% CI: 0.80, 0.98), but at the cost of significantly increased NRM (RR: 1.90, 95% CI: 0.72, 0.87, p=0.0002). There were more deaths during the first remission among patients assigned to autologous HSCT than among the chemotherapy recipients or further untreated patients. As a consequence of increased NRM, no statistical difference in OS (HR: 1.05, 95% CI: 0.91, 1.21) was associated with the use of autologous HSCT, compared to further chemotherapy or no further therapy. These results were concordant with those of the earlier meta-analysis cited above.

A prospective, randomized Phase III trial compared autologous HSCT with intensive consolidation chemotherapy among patients (16-60 years-old) with newly diagnosed AML of similar risk profiles in complete remission (CR1).[16] Patients in CR1 after 2 cycles of intensive chemotherapy (etoposide and mitoxantrone), who were not candidates for allogeneic HSCT, were randomly allocated between a third consolidation cycle of the same chemotherapy (n=259) or autologous HSCT (n=258). The HSCT group showed a trend toward superior relapse-free survival, the primary outcome, compared to chemotherapy recipients (38% vs. 29%, respectively at 5 years, p=0.065, 95% CI: 0.66, 1.1). HSCT patients had a lower relapse rate at 5 years compared to chemotherapy recipients (58% vs. 70%, respectively, p=0.02). Overall survival did not differ between HSCT and chemotherapy recipients, respectively (44% vs. 41%, p=0.86). NRM was more frequent in the autologous HSCT group than in the chemotherapy consolidation group (4% vs. 1%, respectively, p=0.02). Despite this difference in NRM, the relative equality of OS rates was attributed by the investigators to a higher proportion of successful salvage treatments–second-line chemotherapy, autologous or allogeneic HSCT–in the chemotherapy consolidation recipients that were not available to the autologous HSCT patients. This large study shows an advantage for post-remission autologous HSCT in reducing relapse, but similar OS rates secondary to better salvage of chemotherapy-consolidated patients.

The body of evidence summarized in the 2 meta-analyses and randomized controlled trial (RCT) referenced above suggests autologous HSCT to treat AML in CR1 is feasible and potentially offers improved DFS, compared to post-remission chemotherapy in patients who lack a suitable stem-cell donor. However, this procedure is not considered as first-line post-remission therapy for AML patients who are candidates for allogeneic HSCT and for whom a suitable matched donor is available.

Primary Refractory AML

Conventional-dose induction chemotherapy will not produce remission in 20–40% of patients with acute myeloid leukemia (AML), connoting refractory AML. [4] An allogeneic HSCT using a matched related donor (MRD) or matched unrelated donor (MUD) represents the only potentially curative option for

these individuals. In several retrospective studies, OS rates have ranged from 13% at 5 years to 30% at 3 years, although this procedure is accompanied by NRM rates of 25–62% in this setting. [5] For patients who lack a suitable donor (MRD or MUD), 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 such as FLT3 antagonists. Because it is likely that stem-cell preparations will be contaminated with malignant cells in patients whose disease is not in remission, autologous HSCT has no role in patients who fail induction therapy.

Relapsed AML

Most patients with AML will experience disease relapse after attaining a CR1. 4 Conventional chemotherapy is not curative in most patients following disease relapse, even if a second complete remission (CR2) can be achieved. Retrospective data compiled from 667 of 1,540 patients entered in 3 Phase III trials suggest allogeneic HSCT in CR2 can produce 5-year OS rates of 26% to 88%, depending on cytogenetic risk stratification. 19 Because re-induction chemotherapy treatment may be associated with substantial morbidity and mortality, patients whose disease has relapsed and who have a suitable donor may proceed directly to allogeneic HSCT.

In patients without an allogeneic donor, or those who are not candidates for allogeneic HSCT due to age or other factors, autologous HSCT may achieve prolonged DFS in 9–55% of patients in CR2 depending on risk category. 18,20 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 HSCT in this setting is usually limited to individuals who have a sufficient stem-cell preparation remaining from collection in CR1.

Allogeneic HSCT is often performed as salvage for patients who have relapsed after conventional chemotherapy or autologous HSCT. 18 The decision to attempt re-induction or proceed directly to allogeneic HSCT is based on the availability of a suitable stem-cell donor and the likelihood of achieving a remission, the latter being a function of cytogenetic risk group, duration of CR1 and the patient's health status. Registry data show DFS rates of 44% using sibling allografts and 30% with MUD allografts at 5 years for patients transplanted in CR2, and DFS of 35–40% using sibling transplants and 10% with MUD transplants for patients with induction failure or in relapse following HSCT.

Reduced-Intensity Allogeneic HSCT

A growing body of evidence is accruing from clinical studies of RIC with allogeneic HSCT for AML. 2,21-32 Overall, these data suggest that long-term remissions (2–4 years) can be achieved in patients with AML who, because of age or underlying comorbidities would not be candidates for myeloablative conditioning regimens.

A randomized comparative trial in matched patient groups compared the net health benefit of allogeneic HSCT with reduced-intensity conditioning (RIC) versus myeloablative conditioning. 33-35 In this study, patients (age 18-60 years) were randomly assigned to receive either RIC (n=99) of 4 doses of 2 Gy of total-body irradiation and 150 mg/m2 fludarabine or standard conditioning (n=96) of 6 doses of 2 Gy of total-body irradiation and 120 mg/kg cyclophosphamide. All patients received cyclosporin and methotrexate as prophylaxis against graft-versus-host disease. The primary endpoint was the incidence of non-relapse mortality (NRM) analyzed in the intention-to-treat population. This unblinded trial was stopped early because of slow accrual of patients. The incidence of NRM did not differ between the RIC and standard conditioning groups (cumulative incidence at 3 years 13% [95% CI: 6-21] versus 18% [10-26]; HR: 0.62 [95% CI: 0.30-1.31], respectively). Relapse cumulative incidence at 3 years was 28% [95% CI: 19-38] in the RIC group and 26% [17-36]; HR: 1.10 [95% CI: 0.63-1.90]) in the standard conditioning group. Disease-free survival at 3 years was 58% (95% CI: 49-70) in the RIC group and 56% ([46-67]; HR 0.85 [95% CI: 0.55-1.32]) in the standard conditioning group. Overall survival at 3 years was 61% (95% CI: 50-74) and 58% (47-70); HR: 0.77 (95% CI: 0.48-1.25) in the RIC and standard conditioning groups, respectively. No outcomes differed significantly between groups. Grade

3-4 of oral mucositis was less common in the RIC group than in the standard conditioning group (50 patients in the reduced-intensity conditioning group vs. 73 patients in the standard conditioning group); the frequency of other side-effects such as graft-versus-host disease (GVHD) and increased concentrations of bilirubin and creatinine did not differ significantly between groups.

In a recent study, outcomes were compared in children with AML who underwent allogeneic hematopoietic cell transplantation using RIC regimens or myeloablative conditioning regimens.36 A total of 180 patients were evaluated, 39 who underwent RIC and 141 who received myeloablative regimens. Univariate and multivariate analyses showed no significant differences in the rates of acute and chronic GVHD, leukemia-free, and overall survival between treatment groups. The 5-year probabilities of overall survival with RIC and myeloablative regimens were 45% and 48%, respectively (p=0.99). Moreover, relapse rates were not higher with RIC compared with MAC regimens (39% vs 39%; p=0.95), and recipients of MAC regimens were not at higher risk for transplant-related mortality compared with recipients of RIC regimens (16% vs 16%; p=0.73).

A phase II single-center, randomized toxicity study compared myeloablative conditioning and RIC in allogeneic HSCT to treat AML. 37 Adult patients 60 years of age of younger with AML were randomly assigned (1:1) to treatment with RIC (n = 18) or myeloablative conditioning (n = 19) for allogeneic HSCT. A maximum median mucositis grade of 1 was observed in the RIC group compared with 4 in the myeloablative conditioned group (p<0.001). Hemorrhagic cystitis occurred in eight (42%) of the patients in the myeloablative conditioning group and none (0%) in the RIC group (p<0.01). Results of renal and hepatic tests did not differ significantly between the two 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 (TPN) than those treated with myeloablative conditioning (p<0.01). Cytomegalovirus (CMV) infection was more common in the myeloablative conditioning group (14/19) than in the RIC group (6/18) (p=0.02). Donor chimerism was similar in the two groups with regard to CD19 and CD33, but was delayed for CD3 in the RIC group. Five-year TRM was approximately 11% in both groups, and rates of relapse and survival were not significantly different. Patients in the myeloablative conditioning group with intermediate cytogenetic AML had a 3-year survival of 73%, compared with 90% among those in the RIC group.

Indirect comparison of nonrandomized or otherwise comparative study results is compromised by heterogeneity among patients, treatments, outcome measures, and insufficient follow-up. Further, RIC with allogeneic HSCT has not been directly compared with conventional chemotherapy alone, which has been the standard of care in patients with AML for whom myeloablative chemotherapy and allogeneic HSCT are contraindicated.

Allogeneic HSCT with RIC is one of several therapeutic approaches for which evidence exists to show improved health outcomes in patients who could expect to benefit from an allogeneic HSCT. Thus, based on currently available data and clinical input as noted in the following sections, RIC allogeneic HSCT may be considered medically necessary in patients who demonstrate complete marrow and extramedullary remission, who could be expected to benefit from a myeloablative allogeneic HSCT, and who, for medical reasons, would be unable to tolerate a myeloablative conditioning regimen. Additional data are necessary to determine whether some patients with AML and residual disease may benefit from RIC allogeneic HSCT.

Ongoing Clinical Trials
A search of the NCI PDQ in July 2013 identified 37 active or approved Phase III trials in the United States that involve stem-cell support for patients with AML. Trials include allo- and autografting, using various high-dose chemotherapy (HDC) regimens

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers
In response to requests, input was received from 1 physician specialty society (2 reviewers) and 1 academic medical center while this policy was under review for February 2009. While the various physician specialty societies and academic medical centers may collaborate with and make

recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. There was strong consensus among reviewers that RIC allogeneic HSCT was of value in patients who were in complete remission. There was general support for the policy statements.

Summary
A substantial body of published evidence supports the use of allogeneic hematopoietic stem-cell transplantation (HSCT) as consolidation treatment for acute myeloid leukemia (AML) patients in first complete remission (CR1) who have intermediate- or high-risk disease and a suitable donor; this procedure is not indicated for patients in CR1 with good-risk AML.

Data also support the use of allogeneic HSCT for patients in second complete remission (CR2) and beyond who are in chemotherapy-induced remission and for whom a donor is available. Allogeneic HSCT is a consolidation option for those with primary refractory or relapsed disease who can be brought into remission once more with intensified chemotherapy and who have a donor. For patients who are in remission but don't have a suitable donor, evidence supports the use of autologous HSCT in consolidation; this procedure is not an option for those who are not in remission.

Allogeneic HSCT using reduced-intensity conditioning (RIC) is supported by evidence for use in patients who otherwise would be candidates for an allogeneic transplant, but who have comorbidities that preclude use of a myeloablative procedure. These conclusions are generally affirmed in a recent systematic review and analysis of published international guidelines and recommendations, including those of the European Group for Blood and Marrow Transplantation (EBMT), the American Society for Blood and Marrow Transplantation (ASBMT), the British Committee for Standards in Hematology (BCSH), the National Comprehensive Cancer Network, (NCCN), and the specific databases of the National Guideline Clearinghouse and the Guideline International Network database.

Practice Guidelines and Position Statements
The National Comprehensive Cancer Network clinical practice guidelines (V.2.2014) for acute myeloid leukemia are generally consistent with this policy.

U.S. Preventive Services Task Force Recommendations
Hematopoietic stem-cell transplantation is not a preventive service.

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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Billing Coding/Physician Documentation Information

38204 Management of recipient hematopoietic progenitor cell donor search and cell acquisition
38205 Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogenic
38206 Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207 Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208 Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing
38209 Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
38210 Transplant preparation of hematopoietic progenitor cells; specific cell depletion within

harvest, T-cell depletion

38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38220	Bone marrow; aspiration only
38221	Bone marrow; biopsy, needle or trocar
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38240	Bone marrow or blood-derived peripheral stem cell transplantation; allogenic
38241	Bone marrow or blood-derived peripheral stem cell transplantation; autologous
38242	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions
J9000-J9999	Chemotherapy drug code range.
Q0083	Chemotherapy administration by other than infusion technique only (e.g., subcutaneous, intramuscular, push), per visit
Q0084	Chemotherapy administration by infusion technique only, per visit
Q0085	Chemotherapy administration by both infusion technique and other technique(s) (eg, subcutaneous, intramuscular, push), per visit
S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood-derived stem-cell transplantation, allogeneic
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications including pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and post transplant care in the global definition

Additional Policy Key Words

Genetic Testing

Policy Implementation/Update Information

7/1/02	New policy added to the Medical section.
8/1/03	No policy statement changes.
7/1/04	No policy statement changes. Changed from Medical section to Surgery and Transplant sections.
7/1/05	No policy statement changes.
4/1/06	Considerations section revised to include general criteria.
7/1/06	No policy statement changes.
7/1/07	No policy statement changes.
7/1/08	No policy statement changes.
2/12/09	Interim update. Policy statement changed to indicate that, Reduced-intensity conditioning allogeneic SCT may be considered medically necessary as a treatment of AML in patients who are in complete marrow and extramedullary first or second remission, and who for medical reasons, would be unable to tolerate a myeloablative conditioning regimen. Title changed from High Dose Chemotherapy with Hematopoietic Stem Cell Support for Acute Myelogenous Leukemia to Hematopoietic Stem-Cell Transplantation for Acute Myeloid Leukemia
7/1/09	No policy statement changes.
7/1/10	Policy statements revised indicating that allogeneic HSCT may be used in those with poor- to intermediate-risk AML in remission and that allogeneic HSCT may be used after failed autologous HSCT.
7/1/11	No policy statement changes.

1/1/12	Coding updated.
7/1/12	No policy statement changes.
10/1/12	No policy statement changes.
10/1/13	No policy statement changes.
10/1/14	Updated CPT codes. No policy statement changes.
