Name of Policy: Hematopoietic Stem-Cell Transplantation for Acute Myeloid Leukemia

Policy #: 388
Category: Therapy

Latest Review Date: August 2014
Policy Grade: B

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:
1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
**Description of Procedure or Service:**
Acute myeloid leukemia (AML) (also called acute nonlymphocytic leukemia) refers to a set of leukemias that arise from a myeloid precursor in the bone marrow. There is a high incidence of relapse which has prompted research into a variety of post-remission strategies using either allogeneic or autologous hematopoietic stem-cell transplantation (HSCT).

**Hematopoietic Stem-Cell Transplantation**
Hematopoietic stem-cell transplantation (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 radiation therapy. 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”; thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

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 (AML)
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.

The WHO system recognizes five major subcategories of AML: 1) AML with recurrent genetic abnormalities; 2) AML with multilineage dysplasia; 3) therapy-related AML and myelodysplasia (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;q12), 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.

**Policy:**

**Allogeneic hematopoietic stem-cell transplantation (HSCT)** using a myeloablative conditioning regimen **meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage to treat:

- Poor- to intermediate-risk AML in remission (see Policy Guidelines 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 **meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage 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.

**Autologous HSCT meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage to treat AML in first or second remission or relapsed AML if responsive to intensified induction chemotherapy.
Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

**Key Points:**
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 AML in first complete remission (CR1) pooled data from five studies that included a total of 3,100 patients. Among those patients, 1,151 received allogeneic HSCT, 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% CI: 1.06-1.30; p=0.003; random-effects model HR=1.15, 95% confidence interval [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 NCCN outlined in the Policy Guidelines. 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.

Evidence from the meta-analysis cited here suggests patients with cytogetenically 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 three World Health Organization (WHO) cytogenetic prognostic groups that complicates generalization of clinical results based only on cytogenetics. 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 postremission standard chemotherapy as patients with cytogetenically poor-risk AML. Similarly, individuals with cytogetenically 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 have postremission 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. 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]. 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). Inter-study 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 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). Patients younger than 60 years who underwent allogeneic HSCT 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 seven-year OS rate was 58% for the allogeneic HSCT and 46% for the conventional post-remission treatment group (p=0.037; log-rank test). Relapse-free survival was 52% in the allogeneic HSCT group compared with 33% in the control group (p<0.001). OS was significantly better for allogeneic HSCT in 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, postremission therapy was an independent factor for OS (HR=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 examined survival outcomes of autologous HSCT in CR1 versus standard chemotherapy or no further treatment in AML patients aged 15-55 years. 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 4,058 patients
included in six studies, 2,989 (74%) achieved CR1; 1,044 (26%) were randomly allocated to HSCT (n=524) or chemotherapy (n=520). Of the five studies for which OS data were available, outcomes with autologous HSCT were better in three, and outcomes with chemotherapy were better in two. 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 six studies, disease-free survival (DFS) was numerically superior with autologous HSCT compared to chemotherapy (or no further treatment), but only one 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. A total of nine randomized trials involving 1104 adults who underwent autologous HSCT and 1118 who received additional chemotherapy or no additional treatments were identified. The analyses suggest that autologous HSCT in CR1 was associated with statistically significant reduction of relapse 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 recipient or further untreated patients. As a consequence of increased NRM, no statistical difference on 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). Patients in CR1 after two 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 five years, p=0.065, 95% CI: 0.66, 1.1). HSCT patients had a lower relapse rate at five 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 two meta-analyses and 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 who a suitable match donor is available.

**Primary Refractory AML**
Conventional-dose induction chemotherapy will not produce remission in 20%–40% of patients with AML, connoting refractory AML. 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 five years to 30% at three years, although this procedure is accompanied by NRM rates of 25%–62% in this setting. 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 first complete remission. 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 three phase III trials suggest allogeneic HSCT in CR2 can produce five-year OS rates of 26% to 88%, depending on cytogenetic risk stratification. Because reinduction 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% to 55% of patients in CR2 depending on risk category. However, because it is likely that stem-cell preparations will be contaminated with malignant cells in patients whose disease is not in remission and it is often difficult to achieve CR2 in these patients, autologous 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. The decision to attempt reinduction 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 five 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. 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. In this study, patients (age 18-60 years) were randomly assigned to receive either RIC (n=99) of four doses of two Gy of total-body irradiation and 150 mg/m2 fludarabine or standard conditioning (n=96) of six doses of two 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 three years 13% [95% CI: 6-21] versus 18% [10- 26]; HR: 0.62 [95% CI: 0.30-1.31], respectively). Relapse cumulative incidence at three 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 three 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 three 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 HSCT using RIC regimens or myeloablative conditioning regimens. 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 survival, and OS between treatment groups. The five-year probabilities of OS with RIC and myeloablative regimens were 45% and 48%, respectively.
Moreover, relapse rates were not higher with RIC compared with myeloablative conditioning (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 MAC and RIC in allogeneic HSCT to treat AML. Adult patients 60 years of age or younger with AML were randomly assigned (1:1) to treatment with RIC (n=18) or MAC (n=19) for allogeneic HSCT. A maximum median mucositis Grade of 1 was observed in the RIC group compared with four in the MAC group (p<0.001). Hemorrhagic cystitis occurred in eight (42%) of the patients in the MAC 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 than those treated with MAC (p<0.01). Cytomegalovirus infection was more common in the MAC group (14/19) than in the RIC group (6/18) (p=0.02). Donor chimerism was similar in the two groups with regard to 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 were not significantly different. Patients in the MAC group with intermediate cytogenetic AML had a three-year survival of 73%, compared with 90% among those in the RIC group.

Indirect comparison of non-randomized 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 many therapeutic approaches that can be used for which some evidence exists to show improved health outcomes in patients who could be expected to benefit from an allogeneic HSCT. Thus, based on currently available data and clinical input as noted in the following section, 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.

Additional information
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 inter-relates 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:

<table>
<thead>
<tr>
<th>Risk Status of AML Based on Cytogenetic and Molecular Factors</th>
<th>Cytogenetic Factors</th>
<th>Molecular Abnormalities</th>
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<tbody>
<tr>
<td>Better</td>
<td>Inv(16), t(8;21), t(16;16)</td>
<td>Normal cytogenetics with isolated NPM1 mutation</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Normal +8 only, t(9;11) only Other abnormalities not listed with better-risk and poor-risk cytogenetics</td>
<td>c-KIT mutation in patients with t(8;21) or inv(16)</td>
</tr>
<tr>
<td>Poor</td>
<td>Complex (three or more abnormalities) -5, -7, 5q-, 7q-, +8, Inv3, t(3;3), t(6;9), t(9;22) Abnormalities of 11q23, excluding t(9;11)</td>
<td>Normal cytogenetics with isolated FLT3-ITD mutations</td>
</tr>
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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), or non-myeloablative conditioning 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. 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 non-myeloablative conditioning regimen allogeneic HSCT include patients whose age (typically older than 60 years) or comorbidities (e.g., 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, for which there usually is sharing of only three of the six 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.

Summary
A substantial body of published evidence supports the use of allogeneic HSCT as consolidation treatment for AML patients in 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 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 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
National Comprehensive Cancer Network Guidelines
U.S. Preventive Services Task Force Recommendations
Hematopoietic stem-cell transplantation is not a preventive service.

Key Words:
Bone Marrow Transplant, High-Dose Chemotherapy, Acute Myeloid Leukemia (AML), Stem-Cell Transplant

Approved by Governing Bodies:
Not applicable

Benefit Application:
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:
CPT Codes:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>38204</td>
<td>Management of recipient hematopoietic cell donor search and cell acquisition</td>
</tr>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic</td>
</tr>
<tr>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, autologous</td>
</tr>
<tr>
<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing; per donor</td>
</tr>
<tr>
<td>38209</td>
<td>;thawing of previously frozen harvest, with washing; per donor</td>
</tr>
<tr>
<td>38210</td>
<td>;specific cell depletion with harvest, T-cell depletion</td>
</tr>
<tr>
<td>38211</td>
<td>;tumor cell depletion</td>
</tr>
<tr>
<td>38212</td>
<td>;red blood cell removal</td>
</tr>
<tr>
<td>38213</td>
<td>;platelet depletion</td>
</tr>
<tr>
<td>38214</td>
<td>;plasma (volume) depletion</td>
</tr>
<tr>
<td>38215</td>
<td>;cell concentration in plasma, mononuclear, or buffy coat layer</td>
</tr>
<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>38232</td>
<td>; autologous</td>
</tr>
<tr>
<td>38240</td>
<td>Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic</td>
</tr>
</tbody>
</table>
38241 Bone marrow or blood-derived peripheral stem-cell transplantation; autologous
38242 Allogeneic donor lymphocyte infusions

HCPCS:
S2150 Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic, and emergency services)

References:


Policy History:
Medical Policy Group, September 2009 (3)
Medical Policy Administration Committee, September 2009
Available for comment September 18-November 2, 2009
Medical Policy Group, June 2010 (2)
Medical Policy Panel, August 2011
Medical Policy Group, September 2011 (2) Key Points, References updated
Medical Policy Group, December, 2011 (3): 2012 Code Updates: Updated Codes 38208, 38209, and 38230 and added 38232 effective January 1, 2012
Medical Policy Group, August 2012 (3): 2012 Updates to Key Points and References
Medical Policy Panel, August 2013
Medical Policy Group, August 2013 (3): 2013 Updates to Description, Key Points and References; no change in policy statement
Medical Policy Panel, August 2014
Medical Policy Group, September 2014 (3): 2014 Updates to Key Points & References; no change in policy statement

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.