Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

Joint Medical Policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and is therefore subject to change.

***Current Policy Effective Date: 1/1/13**
(See policy history boxes for previous effective dates)

Title: BMT – Hematopoietic Stem-Cell Transplantation for Acute Myeloid Leukemia

Description / Background

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" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD). Cord blood is discussed in greater detail in policy No. 7.01.50.

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 the patient's susceptibility 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

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. AML is characterized by proliferation of myeloblasts, coupled with low production of mature red blood cells, platelets, and often non-lymphocytic white blood cells (granulocytes, monocytes). Clinical signs and symptoms are associated with neutropenia, thrombocytopenia, and anemia. The incidence of AML increases with age, with a median of 67 years. Approximately 13,000 new cases are diagnosed annually.

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 Policy Guidelines).

The WHO system recognizes 5 major subcategories of AML:

1. AML with recurrent genetic abnormalities: 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.
2. AML with multilineage dysplasia: Multilineage dysplasia AML must exhibit dysplasia in 50% or more of the cells of 2 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.
3. Therapy-related AML and myelodysplasia (MDS
4. AML not otherwise categorized: 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.
5. Acute leukemia of ambiguous lineage.

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 approximately 45% of all AML cases. Despite the absence of cytogenetic abnormalities, these cases often have genetic mutations that affect outcomes, 6 of which 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 Guidelines

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:

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. These 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 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.

Regulatory Status

N/A

Medical Policy Statement

The safety and effectiveness of hematopoietic stem-cell transplantation for acute myeloid leukemia has been established. It may be considered a useful therapeutic option for patients meeting specified guidelines.

Contraindications

Absolute and relative contraindications represent situations where proceeding with transplant may not be advisable in the context of limited organ/tissue availability. Contraindications may evolve over time as transplant experience grows in the medical community. Clinical documentation supplied to the health plan *must* demonstrate that attending staff at the transplant center have considered *all* contraindications as part of their overall evaluation of potential organ transplant recipients and have decided to proceed.

Relative contraindications:

The selection process for approved tissue transplants is designed to obtain the best result for each patient. Therefore, relative contraindications to HSCT may include, but are not limited to:

- Poor cardiac function: Ejection fraction should be greater than 45% with no overt symptoms of congestive heart failure.
- Poor pulmonary function: Pulmonary function tests must be greater than or equal to 50% of predicted value.
- Poor renal function: Renal creatinine clearance should be greater than 40 ml/min or creatinine must be less than or equal to 2mg/dl.
- Poor liver function: There should be no history of severe chronic liver disease
- Presence of HIV or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus (HTLV-1).

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions:

- ***Allogeneic* hematopoietic stem-cell transplantation (HSCT) using a *myeloablative* conditioning regimen for patients with:**
  - 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 (NOTE: primary refractory acute myeloid leukemia [AML] is defined as leukemia that

does not achieve a complete remission after conventionally dosed [non-marrow ablative] chemotherapy), or
  - AML in patients who have relapsed following a prior autologous HSCT and are medically able to tolerate the procedure.
- ***Allogeneic* hematopoietic stem-cell transplantation (HSCT) using a *reduced-intensity* conditioning regimen in patients with:**
  - AML who are in complete marrow and extramedullary remission, and who for medical reasons would be unable to tolerate a myeloablative conditioning regimen
- ***Autologous* hematopoietic stem-cell transplantation (HSCT) in patients with:**
  - AML in first or second remission or
  - Relapsed AML if responsive to intensified induction chemotherapy.

Exclusions:
- All other indications not specified under the inclusions.

CPT / HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

38204	38205	38206	38208	38209	38210
38211	38212	38213	38214	38215	38220
38221	38230	38232	38240	38241	38242
S2140	S2142	S2150			

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

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. (2) 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. (3) 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. (4-7) Together, the body of evidence in the context of clinical review of this policy clearly supports the conclusion that myeloablative allogeneic HSCT may be considered medically necessary for patients with poor- to intermediate-risk AML in CR1. Because better-risk AML typically responds well to conventional induction chemotherapy, allogeneic HSCT may be reserved for treatment of relapsed disease in these patients.

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 three World Health Organization (WHO) cytogenetic prognostic groups that complicates generalization of clinical results based only on cytogenetics. (8) 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. (9) 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. (10) 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]. (11) 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 (2) and the current Policy Statements for use of allogeneic HSCT as consolidation therapy for AML.

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. (12) 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 6 studies, 2,989 (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 (13). 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 (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).(14) 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 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 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 AML, connoting refractory AML. (3) 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. (4) 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. (15) 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. (16)

Relapsed AML
Most patients with AML will experience disease relapse after attaining a CR1. (3) 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. (17) 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 9–55% of patients in CR2 depending on risk category. (16, 18) 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. (16)

Allogeneic HSCT is often performed as salvage for patients who have relapsed after conventional chemotherapy or autologous HSCT. (16) 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 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. (16)

Reduced-Intensity Allogeneic HSCT

A growing body of evidence is accruing from clinical studies of RIC with allogeneic HSCT for AML. (1, 19-26) 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. No direct comparative studies with sufficiently long follow-up in matched patient groups are available to define the relative net health benefit of allogeneic HSCT with RIC versus myeloablative treatments. Indirect comparison of 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.

RIC allogeneic HSCT may have many of the same limitations as standard-intensity conditioning HSCT, including relapse, graft-versus-host disease (GVHD, particularly chronic GVHD), and mortality from treatment-related causes other than myelotoxicity. However, this approach is increasingly being used in many centers, comprising an estimated 34% of all allogeneic transplantations in 2005. (27) RIC procedures will continue to evolve and will provide a valuable complement to myeloablative conditioning regimens, extending the benefits of allogeneic HSCT to larger numbers of patients.

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.

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. (28)

Physician Specialty Society and Academic Medical Center Input
In response to requests, Blue Cross Blue Shield Association received input 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.

2011 National Comprehensive Cancer Network Guidelines
The National Comprehensive Cancer Network clinical practice guidelines (V.2.2012) for acute myeloid leukemia are generally consistent with this policy. Available online at: http://www.nccn.org/professionals/physician_gls/PDF/aml.pdf.

National Cancer Institute (NCI) Clinical Trial Database (PDQ®)
A search of the NCI PDQ ☐ in July 20
United States that involve stem-cell support for patients with AML. Trials include allo- and autografting, using various HDC regimens.

Government Regulations
National:
National Coverage Determination (NCD) for Stem Cell Transplantation (110.8.1), Effective Date of this Version 8/4/10, Implementation Date 11/10/10, Retrieved from: http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=45&ncdver=5&bc=AgAAgAAAAAAA&, Accessed 7/31/12.

Indications and Limitations of Coverage
1. **Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)**

Allogeneic hematopoietic stem cell transplantation (HSCT) is a procedure in which a portion of a healthy donor's stem cell or bone marrow is obtained and prepared for intravenous infusion.

a. Nationally Covered Indications

The following uses of allogeneic HSCT are covered under Medicare:

i. Effective for services performed on or after August 1, 1978, for the treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary,

ii. Effective for services performed on or after June 3, 1985, for the treatment of severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome.

iii. Effective for services performed on or after August 4, 2010, for the treatment of Myelodysplastic Syndromes (MDS) pursuant to Coverage with Evidence Development (CED) in the context of a Medicare-approved, prospective clinical study.

2. Autologous Stem Cell Transplantation (AuSCT)

Autologous stem cell transplantation (AuSCT) is a technique for restoring stem cells using the patient's own previously stored cells.

a. Nationally Covered Indications

i. Effective for services performed on or after April 28, 1989, AuSCT is considered reasonable and necessary under §l862(a)(1)(A) of the Social Security Act (the Act) for the following conditions and is covered under Medicare for patients with:

- Acute leukemia in remission who have a high probability of relapse and who have no human leucocyte antigens (HLA)-matched;
- Resistant non-Hodgkin's lymphomas or those presenting with poor prognostic features following an initial response;
- Recurrent or refractory neuroblastoma; or
- Advanced Hodgkin's disease who have failed conventional therapy and have no HLA-matched donor.

ii. Effective October 1, 2000, single AuSCT is only covered for Durie-Salmon Stage II or III patients that fit the following requirements:

- Newly diagnosed or responsive multiple myeloma. This includes those patients with previously untreated disease, those with at least a partial response to prior chemotherapy (defined as a 50% decrease either in measurable paraprotein [serum and/or urine] or in bone marrow infiltration, sustained for at least 1 month), and those in responsive relapse; and,
- Adequate cardiac, renal, pulmonary, and hepatic function.

iii. Effective for services performed on or after March 15, 2005, when recognized clinical risk factors are employed to select patients for transplantation, high dose melphalan (HDM) together with AuSCT is reasonable and necessary for Medicare beneficiaries of any age group with primary amyloid light chain (AL) amyloidosis who meet the following criteria:

- Amyloid deposition in 2 or fewer organs; and,
- Cardiac left ventricular ejection fraction (EF) greater than 45%.

b. Nationally Non-Covered Indications

Insufficient data exist to establish definite conclusions regarding the efficacy of AuSCT for the following conditions:

- Acute leukemia not in remission;
- Chronic granulocytic leukemia;
- Solid tumors (other than neuroblastoma);
- Up to October 1, 2000, multiple myeloma;
- Tandem transplantation (multiple rounds of AuSCT) for patients with multiple myeloma;
- Effective October 1, 2000, non primary AL amyloidosis; and,
- Effective October 1, 2000, thru March 14, 2005, primary AL amyloidosis for Medicare beneficiaries age 64 or older.

In these cases, AuSCT is not considered reasonable and necessary within the meaning of §l862(a)(1)(A) of the Act and is not covered under Medicare.

Other
All other indications for stem cell transplantation not otherwise noted above as covered or non-covered nationally remain at local contractor discretion.

Local:
There is no local coverage determination on this topic.

Michigan Department of Community Health:
Medicaid Provider Manual, Version Date: April 1, 2012, Retrieved from http://www.mdch.state.mi.us/dch-medicaid/manuals/MedicaidProviderManual.pdf, Accessed: 7/31/12.

6.6 Transplants
Heart, bone marrow, liver, lung, simultaneous pancreas/kidney and pancreas transplants are reimbursed at the hospital's Medicaid cost to charge ratio.

- Organ acquisition costs are reimbursed at 100% of charges when billed using either revenue code 0811 or 0812. This applies to heart, kidney, liver, lung, simultaneous pancreas/kidney, or pancreas transplants. **This does not apply to bone marrow transplants. All bone marrow transplant charges are reimbursed at the hospital's cost to charge ratio.**
- The letter of authorization for the transplant from the Office of Medical Affairs (OMA) or MHP must be attached to all transplant claims, otherwise, payment is denied.
- Indicate "PA letter submitted" in the Remarks Section of the submitted claim.
- For other transplant services not described by a specific DRG, identify in the Remarks Section the type of transplant that has been performed (i.e., small bowel transplant).
- If the donor and beneficiary are both Medicaid eligible, the services must be billed under each beneficiary's respective ID Number. If only the beneficiary is Medicaid eligible, bill services for both donor and beneficiary under the Medicaid beneficiary's ID Number.

All other insurance resources must be exhausted before Medicaid is billed. If Medicare eligibility is denied, the denial notice must be submitted with the claim.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- BMT – Autologous, for Malignant Astrocytomas and Gliomas
- BMT – Hematopoietic Stem Cell Transplantation for Breast Cancer
- BMT – Hematopoietic Stem Cell Transplantation for Treatment of Multiple Myeloma
- BMT – Hematopoietic Stem Cell Transplantation for Acute Lymphoblastic Leukemia
- BMT – Hematopoietic Stem Cell Transplantation for Autoimmune Diseases
- BMT – Hematopoietic Stem Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma - Autologous or Allogeneic
- BMT – Hematopoietic Stem Cell Transplantation for Chronic Myelogenous Leukemia
- BMT – Hematopoietic Stem Cell Transplantation for CNS Embryonal Tumors and Ependymoma
- BMT – Hematopoietic Stem Cell Transplantation for Epithelial Ovarian Cancer
- BMT – Hematopoietic Stem Cell Transplantation for Hodgkin Lymphoma
- BMT – Hematopoietic Stem Cell Transplantation for Miscellaneous Solid Tumors in Adults
- BMT – Hematopoietic Stem Cell Transplantation for Non-Hodgkin Lymphomas
- BMT – Hematopoietic Stem Cell Transplantation for Primary Amyloidosis
- BMT – Hematopoietic Stem Cell Transplantation for Solid Tumors of Childhood
- BMT – Hematopoietic Stem Cell Transplantation for Waldenström's Macroglobulinemia
- BMT – Hematopoietic Stem Cell Transplantation in the Treatment of Germ-Cell Tumors
- Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Stem-Cell Transplant

---

References

1. Hamadani M, Mohty M, Kharfan-Dabaja MA. Reduced-intensity conditioning allogeneic hematopoietic cell transplantation in adults with acute myeloid leukemia. Cancer Control 2011; 18(4):237-45.
2. Yanada M, Matsuo K, Emi N et al. Efficacy of allogeneic hematopoietic stem cell transplantation depends on cytogenetic risk for acute myeloid leukemia in first disease remission: a metaanalysis. Cancer 2005; 103(8):1652-8.
3. Greer JP, Foerster J, Rodgers GM et al., eds. Acute myeloid leukemia in adults. In *Wintrobe's Clinical Hematology.* 12th ed. Philadelphia: Lippincott Williams & Wilkins, 2009.
4. Hamadani M, Awan FT, Copelan EA. Hematopoietic stem cell transplantation in adults with acute myeloid leukemia. Biol Blood Marrow Transplant 2008; 14(5):556-67.
5. Deschler B, de Witte T, Mertelsmann R et al. Treatment decision-making for older patients with high-risk myelodysplastic syndrome or acute myeloid leukemia: problems and approaches. Haematologica 2006; 91(11):1513-22.
6. Craddock CF. Full-intensity and reduced-intensity allogeneic stem cell transplantation in AML. Bone Marrow Transplant 2008; 41(5):415-23.
7. Cornelissen JJ, van Putten WL, Verdonck LF et al. Results of a HOVON/SAKK donor versus no-donor analysis of myeloablative HLA-identical sibling stem cell transplantation in first remission acute myeloid leukemia in young and middle-aged adults: benefits for whom? Blood 2007; 109(9):3658-66.
8. Mrozek K, Bloomfield CD. Chromosome aberrations, gene mutations and expression changes, and prognosis in adult acute myeloid leukemia. Hematology Am Soc Hematol Educ Program 2006:169-77.

9. Paschka P, Marcucci G, Ruppert AS et al. Adverse prognostic significance of KIT mutations in adult acute myeloid leukemia with inv(16) and t(8;21): a Cancer and Leukemia Group B Study. J Clin Oncol 2006; 24(24):3904-11.
10. Schlenk RF, Dohner K, Krauter J et al. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. N Engl J Med 2008; 358(18):1909-18.
11. Koreth J, Schlenk R, Kopecky KJ et al. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials. JAMA 2009; 301(22):2349-61.
12. Nathan PC, Sung L, Crump M et al. Consolidation therapy with autologous bone marrow transplantation in adults with acute myeloid leukemia: a meta-analysis. J Natl Cancer Inst 2004; 96(1):38-45.
13. Wang J, Ouyang J, Zhou R et al. Autologous hematopoietic stem cell transplantation for acute myeloid leukemia in first complete remission: a meta-analysis of randomized trials. Acta Haematol 2010; 124(2):61-71.
14. Vellenga E, van Putten W, Ossenkoppele GJ et al. Autologous peripheral blood stem cell transplantation for acute myeloid leukemia. Blood 2011; 118(23):6037-42.
15. Estey EH. Treatment of acute myeloid leukemia. Haematologica 2009; 94(1):10-6.
16. Stone RM, O'Donnell MR, Sekeres MA. Acute myeloid leukemia. Hematology Am Soc Hematol Educ Program 2004:98-117.
17. Breems DA, Van Putten WL, Huijgens PC et al. Prognostic index for adult patients with acute myeloid leukemia in first relapse. J Clin Oncol 2005; 23(9):1969-78.
18. Breems DA, Lowenberg B. Acute myeloid leukemia and the position of autologous stem cell transplantation. Semin Hematol 2007; 44(4):259-66.
19. Oliansky DM, Appelbaum F, Cassileth PA et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute myelogenous leukemia in adults: an evidence-based review. Biol Blood Marrow Transplant 2008; 14(2):137-80.
20. Blaise D, Vey N, Faucher C et al. Current status of reduced-intensity-conditioning allogeneic stem cell transplantation for acute myeloid leukemia. Haematologica 2007; 92(4):533-41.
21. Huisman C, Meijer E, Petersen EJ et al. Hematopoietic stem cell transplantation after reduced intensity conditioning in acute myelogenous leukemia patients older than 40 years. Biol Blood Marrow Transplant 2008; 14(2):181-6.
22. Valcarcel D, Martino R. Reduced intensity conditioning for allogeneic hematopoietic stem cell transplantation in myelodysplastic syndromes and acute myelogenous leukemia. Curr Opin Oncol 2007; 19(6):660-6.
23. Valcarcel D, Martino R, Caballero D et al. Sustained remissions of high-risk acute myeloid leukemia and myelodysplastic syndrome after reduced-intensity conditioning allogeneic hematopoietic transplantation: chronic graft-versus-host disease is the strongest factor improving survival. J Clin Oncol 2008; 26(4):577-84.
24. Gyurkocza B, Storb R, Storer BE et al. Nonmyeloablative allogeneic hematopoietic cell transplantation in patients with acute myeloid leukemia. J Clin Oncol 2010; 28(17):2859-67.
25. McClune BL, Weisdorf DJ, Pedersen TL et al. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. J Clin Oncol 2010; 28(11):1878-87.
26. Lim Z, Brand R, Martino R et al. Allogeneic hematopoietic stem-cell transplantation for patients 50 years or older with myelodysplastic syndromes or secondary acute myeloid leukemia. J Clin Oncol 2010; 28(3):405-11.

27. Gratwohl A, Baldomero H, Frauendorfer K et al. Results of the EBMT activity survey 2005 on haematopoietic stem cell transplantation: focus on increasing use of unrelated donors. Bone Marrow Transplant 2007; 39(2):71-87.
28. Hubel K, Weingart O, Naumann F et al. Allogeneic stem cell transplant in adult patients with acute myelogenous leukemia: a systematic analysis of international guidelines and recommendations. Leuk Lymphoma 2011; 52(3):444-57.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through August 1, 2012, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/13	10/16/12	10/16/12	• Topic split out from former combined autologous and allogeneic bone marrow transplant policies. • Policy formatted to mirror BCBSA. • Added “relative contraindications” to inclusionary/exclusionary section.

Next Review Date: 4th Qtr, 2013

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: BMT – HEMATOPOIETIC STEM-CELL TRANSPLANTATION FOR ACUTE MYELOID LEUKEMIA

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	Refer to Medicare section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.
Blue Cross Complete of Michigan	Refer to Medicare section.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.