

Corporate Medical Policy

Hematopoietic Stem-Cell Transplantation for Acute Myeloid Leukemia

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Description of Procedure or Service

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 the Cord Blood as a Source of Stem Cells medical policy.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA A, B, and DR loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

Conventional Preparative Conditioning for HSCT

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

The success of autologous HSCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient prior to undergoing bone marrow ablation. As a consequence, autologous HSCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and

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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 total 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. (see Policy Guidelines)

The WHO system recognizes 5 major subcategories of AML: 1) AML with recurrent genetic abnormalities; 2) AML with multilineage dysplasia; 3) therapy-related AML and myelodysplasia (MDS); 4) AML not otherwise categorized; and 5) acute leukemia of ambiguous lineage. AML with recurrent genetic abnormalities includes AML with t(8;21)(q22;q22), inv(16)(p13;q22) or t(16;16)(p13;q22), t(15;17)(q22;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

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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.

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for Hematopoietic Stem-cell Transplantation for Acute Myeloid Leukemia (AML) when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Some patients may be eligible for coverage under Clinical Trials. Refer to the policy on Clinical Trial Services for Life-Threatening Conditions.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

Some health benefit plans may exclude benefits for transplantation.

When Hematopoietic Stem-Cell Transplantation for Acute Myeloid Leukemia is covered

1. Allogeneic hematopoietic stem-cell transplantation (HSCT) using a myeloablative conditioning regimen may be considered medically necessary to treat:
 - a. Poor- to intermediate-risk AML in remission, or
 - b. AML that is refractory to, or relapses following standard induction chemotherapy, or
 - c. AML in patients who have relapsed following a prior autologous HSCT and are medically able to tolerate the procedure.
2. Allogeneic HSCT using a reduced-intensity conditioning regimen may be considered medically necessary as a treatment of AML in patients who are in complete marrow and extramedullary remission, and who for medical reasons would be unable to tolerate a myeloablative conditioning regimen.
3. Autologous HSCT may be considered medically necessary to treat AML in first or second remission or relapsed AML if responsive to intensified induction chemotherapy.

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When Hematopoietic Stem-Cell Transplantation for Acute Myeloid Leukemia it is not covered

Hematopoietic stem-cell transplantation for acute myeloid leukemia is considered not medically necessary when the medical criteria listed above are not met.

Policy Guidelines

Refer to the individual member's benefit booklet for prior review requirements.

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

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

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

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

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

Risk Status of AML Based on Cytogenetic and Molecular Factors

Risk Status	Cytogenetic Factors	Molecular Abnormalities
Better	Inv(16), t(8;21), 5(16;16)	Normal cytogenetics with isolated NPM1 mutation
Intermediate	Normal +8 only, 5(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), 5(6;9), t(9;22)	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

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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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable Codes: 38205, 38206, 38230, 38232, 38240, 38241, 38242, S2150

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual, 12/1/1999; 8.01.26

BCBSA Medical Policy Reference Manual, 8/18/2000; 8.01.26

Specialty Matched Consultant Advisory Panel - 11/2002

BCBSA Medical Policy Reference Manual [Electronic]. 8.01.26, 12/18/2002

Specialty Matched Consultant Advisory Panel - 11/2004

BCBSA Medical Policy Reference Manual [Electronic]. 8.01.26, 9/27/2005

Specialty Matched Consultant Advisory Panel - 3/2006

BCBSA Medical Policy Reference Manual [Electronic]. 8.01.26, 4/17/07

Specialty Matched Consultant Advisory Panel - 3/2008

BCBSA Medical Policy Reference Manual [Electronic]. 8.01.26, 5/14/09

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Acute myeloid leukemia. Retrieved 8/4/09 from http://www.nccn.org/professionals/physician_gls/PDF/aml.pdf

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Specialty Matched Consultant Advisory Panel – 5/2010

BCBSA Medical Policy Reference Manual [Electronic]. 8.01.26, 6/10/2010

Specialty Matched Consultant Advisory Panel – 4/2011

BCBSA Medical Policy Reference Manual [Electronic]. 8.01.26, 8/11/2011

Specialty Matched Consultant Advisory Panel – 4/2012

Policy Implementation/Update Information

- 1/01 Specialty Matched Consultant Advisory Group.
- 2/01 Original Policy Issued.
- 2/03 Specialty Matched Consultant Advisory Panel review 11/2002. No change in criteria. Codes 86812-86822 removed; codes 38231 and 86915 deleted and codes 38242, 38205 and 38206 added to the Billing/Coding section. System coding changes.
- 1/04 Benefits Application and Billing/Coding sections updated for consistency.
- 2/04 Individual CPT codes listed for CPT code ranges, 38240-38242 under Billing/Coding section.
- 7/29/04 HCPCS code S2150 added to Billing/Coding section.
- 12/9/04 Specialty Matched Consultant Advisory Panel review 11/29/2004. No changes to criteria. Revised Description of Procedure or Service section. Added policy number to Policy Key Words section. "Hematopoietic" and "Opportunistic" added to Definitions. References added.
- 4/10/06 Specialty Matched Consultant Advisory Panel review 3/15/2006. No changes to policy. References added.
- 6/2/08 Specialty Matched Consultant Advisory Panel review 3/17/08. Added reference to the Clinical Trials policy to the "Policy" section. Changed wording in the "When Covered" section #2.e. from "such as" to "including but not limited to". References added.
- 9/14/09 Reviewed with Senior Medical Director 8/26/09. Policy named changed from "Bone Marrow Transplant for Acute Myelogenous Leukemia" to "Hematopoietic Stem-Cell Transplant for Acute Myelogenous Leukemia". Description revised. Removed reference to "Bone Marrow Transplant, high dose chemotherapy and stem cell support" and inserted "hematopoietic stem-cell transplantation" in the "Policy" section. Completely revised the "When Covered" section to indicate; "1. Allogeneic hematopoietic stem-cell transplantation (HSCT) using a myeloablative conditioning regimen may be considered medically necessary to treat: a) Poor- to intermediate-risk AML in remission, or b) AML that is refractory to, or relapses following standard induction chemotherapy, or c) AML in patients who have relapsed following a prior autologous HSCT and are medically able to tolerate the procedure. 2. Allogeneic HSCT using a reduced-intensity conditioning regimen may be considered medically necessary as a treatment of AML in patients who are in complete marrow and extramedullary remission, and who for medical reasons would be unable to tolerate a myeloablative conditioning regimen. 3. Autologous HSCT may be considered medically necessary to treat AML in first or second remission or relapsed AML if responsive to intensified induction chemotherapy." Updated "Policy Guidelines" section. References added. (btw)
- 6/22/10 Policy Number(s) removed. (amw)
- 7/6/10 Specialty Matched Consultant Advisory Panel review 5/24/2010. Changed the title from "Myelogenous" to "Myeloid". Removed the following statement; "Services for or related to the search for a donor is not covered." From the "Benefits Application" section. No changes to

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policy statement. References added. (btw)

5/24/11 Specialty Matched Consultant Advisory Panel review 4/27/11. No change to policy intent. Added the Risk Status of AML Based on Cytogenetic and Molecular Factors table to the “Policy Guidelines” section. Removed the following statements from the “Policy Guidelines” section; “While some high dose chemotherapy (HDC) protocols can be administered on an outpatient basis, typically the patient is hospitalized for management of the marrow ablative complications of the therapy.” and “All patients receiving whole body radiotherapy, typically those receiving an allogeneic transplant (from donor to patient), will require prolonged hospitalization.”
References added. (btw)

2/21/12 New 2012 CPT code 38232 added to Billing/Coding section. (btw)

5/15/12 Specialty Matched Consultant Advisory Panel review 4/18/2012. Changed the “When Not Covered” section from “investigational” to “Hematopoietic stem-cell transplantation for acute myeloid leukemia is considered not medically necessary when the medical criteria listed above are not met.” Policy Guidelines updated. Reference added. (btw)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.