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Title

Hematopoietic Stem cell Transplantation for Acute Myeloid Leukemia

Description

Hematopoietic Stem-Cell Transplantation¹

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).

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 5 major subcategories of AML: 1) AML with recurrent genetic abnormalities; 2) AML with multilineage dysplasia; 3) therapy-related AML and myelodysplasia (MDS); 4) AML not otherwise categorized; and 5) acute leukemia of ambiguous lineage. AML with recurrent genetic abnormalities includes AML with t(8;21)(q22;q22), inv(16)(p13;q22) or t(16;16)(p13;q22), t(15;17)(q22;aq12), or translocations or structural abnormalities involving 11q23. Younger patients may exhibit t(8;21) and inv(16) or t(16;16). AML patients with 11q23 translocations include two subgroups: AML in infants and therapy-related leukemia. Multilineage dysplasia AML must exhibit dysplasia in 50% or more of the cells of two lineages or more. It is associated with cytogenetic findings that include -7/del(7q), -5/del(5q), +8, +9, +11, del(11q), del(12p), -18, +19, del(20q)+21, and other translocations. AML not otherwise categorized includes disease that does not fulfill criteria for the other groups, and essentially reflects the morphologic and cytochemical features and maturation level criteria used in the FAB classification, except for the definition of AML as having a minimum 20% (as opposed to 30%) blasts in the marrow. AML of ambiguous lineage is diagnosed when blasts lack sufficient lineage-specific antigen expression to classify as myeloid or lymphoid.

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

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

When services are covered for both commercial products and for Medicare HMO Blue, Medicare PPO Blue and Blue Medicare PFFS PlusRx products

- We cover allogeneic hematopoietic stem-cell transplantation (HSCT) using a myeloablative conditioning regimen to treat:
poor- to intermediate-risk AML in remission 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.
- We cover allogeneic HSCT using a reduced-intensity conditioning regimen 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.
- We cover autologous HSCT to treat AML in first or second remission or relapsed AML if responsive to intensified induction chemotherapy.

Note:

- We cover stem cells when harvested from the patient's bone marrow prior to marrow ablative therapy or from a donor's marrow after verifying the donor and recipient are well matched with respect to human leukocyte antigens (HLA). Verification of well matched HLA donor and recipient is based on the attending or treating physician's clinical judgment.
- For diagnoses listing number of antigen matches (i.e. sickle cell anemia, aplastic anemia, beta thalassemia major, SCID, Wiskott-Aldrich syndrome, Infantile Malignant Osteopetrosis, Mucopolysaccharidosis, and Mucopolipidoses), we cover stem cells when the specific matching is met. (refer to specific diagnoses above)

Criteria for use of umbilical cord blood as a source of stem cells

We cover **umbilical cord stem cell support** as an acceptable cell source for transplants that are otherwise covered for either high-dose chemo with stem cell support, or for bone marrow transplant, when all the following are met:

- Recipient is a child or adult
- There is no other available stem-cell donor with the same or better matching characteristics
- Donors may be related or unrelated.

We cover collection and storage of cord blood from neonate when an allogeneic transplant is "imminent" in an identified recipient with a diagnosis that is consistent with the possible need for allogeneic transplant.

Exclusions:

- Facility providing umbilical cord blood that is not in compliance with any existing FDA regulations governing umbilical cord transplants. FDA regulations are currently under development
- There is a suitable stem cell donor of equal or superior HLA match
- Storage for future use, in case of a future need for transplant (prophylactic collection and storage).

Criteria for use of peripheral blood as a source of stem cells

- We cover peripheral blood stem cells when harvested from an HLA-matched allogeneic donor.
- We cover stem cells when harvested from the patient's bone marrow prior to marrow ablative therapy or from a donor's marrow after verifying the donor and recipient are well matched with respect to human leukocyte antigens (HLA). Verification of well matched HLA donor and recipient is based on the attending or treating physician's clinical judgment.

- For diagnoses listing number of antigen matches (i.e. sickle cell anemia, aplastic anemia, beta thalassemia major, SCID, Wiskott-Aldrich syndrome, Infantile Malignant Osteopetrosis, Mucopolysaccharidosis, and Mucopolipidoses), we cover stem cells when the specific matching is met. (refer to specific diagnoses above)

When services are not covered for both commercial products or for Medicare HMO Blue, Medicare PPO Blue and Blue Medicare PFFS PlusRx products

There are no indications for coverage other than those listed above.

Individual consideration

All our medical policies are written for the majority of people with a given condition. Each policy is based on medical science. For many of our medical policies, each individual's unique clinical circumstances may be considered in light of current scientific literature. For consideration of an individual patient, physicians may send relevant clinical information to:

For services already billed

Blue Cross Blue Shield of Massachusetts
 Provider Appeals
 PO Box 986065
 Boston, MA 02298

Prior to performance of service

Blue Cross Blue Shield of Massachusetts
 Case Creation/Medical Policy
 One Enterprise Drive
 Quincy, MA 02171
 Tel: 1-800-327-6716
 Fax: 1-888-641-5330

Authorization Information

For Managed Care members:

- Authorization is required for this service; see *Managed Care Guidelines* for additional requirements.

For Indemnity and PPO members:

- Authorization is required for this service; see *Indemnity and PPO Guidelines* for additional requirements.

Managed Care Guidelines

All authorization requirements are determined by the individual's subscriber certificate, explanation of coverage, or summary plan description, however;

- **For Medicare HMO Blue members:** The service must meet the criteria for coverage noted in this policy, be medically necessary, prescribed by a plan physician and provided by a network provider.
- **For Medicare HMO Blue members:** Referrals are required for all visits to a specialist.
- For all other Managed Care plans, any specialist visit requires a referral, except for visits performed by OB/GYN specialists.
- Authorization is required for an inpatient admission.

Indemnity and PPO Guidelines

All authorization requirements are determined by the individual's subscriber certificate, explanation of coverage, or summary plan description, however;

- Authorization is required for an inpatient admission.
- Authorizations are not required for most outpatient services as determined by the individual's subscriber certificate.
- Referrals to a specialist are not required.

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

Risk Status of AML Based on Cytogenetic and Molecular Factors

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

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

Some patients for whom a conventional myeloablative allogeneic transplant could be curative may be considered candidates for reduced-intensity conditioning (RIC) allogeneic HSCT. These include those 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 his or her medical status would permit it. However, this type of patient would likely undergo RIC prior to a second allogeneic HSCT if a complete remission could be re-induced with chemotherapy.

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

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

Clinical trials for Cancer Mandate²

As required by law, we provide coverage for services and supplies received as part of a qualified clinical trial (for treatment of cancer) when the member is enrolled in that trial. This coverage is provided for services and supplies that are consistent with the study protocol and with the standard of care for someone with the patients' diagnosis, and that would be covered if the patient did not participate in the trials. This coverage may also be provided for investigational drugs and devices that have been approved for use as part of the trial. Coverage for services and supplies that are received as part of a qualified clinical trial is provided to the same extent as it would have been provided if the patient did not participate in the trial.

However, no coverage is provided for:

- Investigational drugs and devices that have not been approved for use in the trial.
- Investigational drugs and devices that are paid for by the manufacturer, distributor or provider of the drug or device, whether or not the drug or device has been approved for use in the trial.
- Non-covered services under the member's contract.
- Costs associated with managing the research for the trial.
- Items, services or costs that are reimbursed or otherwise furnished by the sponsor of the trial.
- Costs of services that are inconsistent with widely accepted and established national and regional standards of care.
- Costs of clinical trials that are not "qualified trials."

According to the subscriber certificate, benefits are provided for covered transplant services only when they are furnished to a recipient who is an enrolled member. However, benefits will be provided for the harvesting of the donor's organ (or stem cells) when the donor is a not member as long as the recipient is a member. "Harvesting" includes the surgical removal of the donor's organ (or stem cells) and related medically necessary services and/or tests that are required to perform the transplant itself.

Coding information

Procedure codes are from current CPT, HCPCS Level II, Revenue Code, and/or ICD-9-CM manuals, as recommended by the American Medical Association, Centers for Medicare and Medicaid Services and American Hospital Associations. Blue Cross Blue Shield Association national codes may be developed when appropriate.

The following codes are included below for informational purposes. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

CPT codes:

- **38230:** Bone marrow harvesting for transplantation
- **38240:** Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic
- **38241:** Bone marrow or blood-derived peripheral stem-cell transplantation; autologous
- **38242:** Allogeneic donor lymphocyte infusions

HCPCS codes:

- **Q0083 - Q0085:** Chemotherapy administration code range
- **J9000 - J9999:** Chemotherapy drug code range
- **S2140:** Cord blood harvesting for transplantation, allogeneic
- **S2142:** Cord blood derived stem-cell transplantation, allogeneic
- **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)

Policy update history

New policy, based on BCBSA policy 8.01.26 and corresponding information removed from BCBSMA policies #092, Allogeneic Stem Cell Transplantation and #126, Autologous Stem Cell Transplantation, effective **09/01/09**.

References

References for footnote 1:

1. 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.
2. Baer MR, Greer JP. Acute myeloid leukemia in adults. In: Greer JP, Foerster J, Rodgers GM et al. (eds.). *Wintrobe's Clinical Hematology*. Philadelphia, Lippincott Williams & Wilkins, 2009.
3. 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.
4. Deschler B, de Witte T, Mertelsman 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.
5. Craddock CF. Full-intensity and reduced-intensity allogeneic stem cell transplantation in AML. *Bone Marrow Transplant* 2008; 41(5):415-23.
6. 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.
7. 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.
8. 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.
9. 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.
10. 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.
11. Estey EH. Treatment of acute myeloid leukemia. *Haematologica* 2009; 94(1): 10-16.
12. Stone RM, O'Donnell MR, Sekeres MA. Acute myeloid leukemia. *Hematology Am Soc Hematol Educ Program* 2004; 98-117
13. 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.
14. Breems DA, Lowenberg B. Acute myeloid leukemia and the position of autologous stem cell transplantation. *Semin Hematol* 2007; 44(4):259-66.
15. 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.
16. 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.
17. Valcarcel D, Martino R. Reduced intensity conditioning for allogeneic hematopoietic stem cell transplantation in myelodysplastic syndromes and acute myelogenous leukemia. *Current Opin Oncol* 2007; 19(6):660-6.
18. 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.

19. Oliansky DM, Appelbaum F, Cassileth PA et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute myeloid leukemia in adults: an evidence-based review. *Biol Blood Marrow Transplant* 2008; 14(2):137-80
20. 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.
21. Acute Myeloid Leukemia. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. v.1.2009 http://www.nccn.org/professionals/physician_gls/PDF/aml.pdf (accessed April 2009)

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Footnotes

¹ Based on BCBSA policy # 8.01.26, issued 5/09.

² Based on MGL - Chapter 118G, Section 1