MASSACHUSETTS

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Medical Policy

Hematopoietic Cell Transplantation for Acute Myeloid Leukemia

Table of Contents

Policy Number: 150

BCBSA Reference Number: 8.01.26
NCD/LCD: N/A

Related Policies

- Genetic Testing for *FLT3*, *NPM1*, and *CEBPA* Variants in Acute Myeloid Leukemia #693
- Placental and Umbilical Cord Blood as a Source of Stem Cells #285

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue[SM] and Medicare PPO Blue[SM] Members

Allogeneic hematopoietic stem-cell transplantation (HCT) using a myeloablative conditioning regimen may be **MEDICALLY NECESSARY** to treat:

- Poor- to intermediate-risk acute myeloid leukemia (AML) in remission
- AML that is refractory to standard induction chemotherapy but can be brought into CR with intensified induction chemotherapy
- AML that relapses following chemotherapy-induced CR1 but can be brought into CR2 or beyond with intensified induction chemotherapy; or
- AML in patients, who have relapsed following a prior autologous (HCT), but can be brought into CR with intensified induction chemotherapy and are medically able to tolerate the procedure.

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

Allogeneic (HCT) using a reduced-intensity conditioning regimen be **MEDICALLY NECESSARY** as a treatment of AML in patients who are in complete marrow and extramedullary remission (CR1 or beyond), and who for medical reasons would be unable to tolerate a myeloablative conditioning regimen.

Autologous (HCT) may be **MEDICALLY NECESSARY** to treat AML in CR1 or beyond, or relapsed AML, if responsive to intensified induction chemotherapy.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is **required**.
Commercial PPO and Indemnity	Prior authorization is **required**.
Medicare HMO Blue℠	Prior authorization is **required**.
Medicare PPO Blue℠	Prior authorization is **required**.

CPT Codes / HCPCS Codes / ICD Codes

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.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

CPT codes:	Code Description
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation

HCPCS codes

HCPCS codes:	Code Description
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)

ICD-10 Procedure Codes

ICD-10-PCS procedure codes:	Code Description
30233G0	Transfusion of Autologous Bone Marrow into Peripheral Vein, Percutaneous Approach
30233G1	Transfusion of Nonautologous Bone Marrow into Peripheral Vein, Percutaneous Approach
30233X1	Transfusion of Nonautologous Cord Blood Stem Cells into Peripheral Vein, Percutaneous Approach
30233Y0	Transfusion of Autologous Hematopoietic Stem Cells into Peripheral Vein, Percutaneous Approach
30233Y1	Transfusion of Nonautologous Hematopoietic Stem Cells into Peripheral Vein, Percutaneous Approach
30243G0	Transfusion of Autologous Bone Marrow into Central Vein, Percutaneous Approach
30243G1	Transfusion of Nonautologous Bone Marrow into Central Vein, Percutaneous Approach
30243X1	Transfusion of Nonautologous Cord Blood Stem Cells into Central Vein, Percutaneous Approach
30243Y0	Transfusion of Autologous Hematopoietic Stem Cells into Central Vein, Percutaneous Approach
30243Y1	Transfusion of Nonautologous Hematopoietic Stem Cells into Central Vein, Percutaneous Approach
30263G0	Transfusion of Autologous Bone Marrow into Central Artery, Percutaneous Approach
30263G1	Transfusion of Nonautologous Bone Marrow into Central Artery, Percutaneous Approach
30263X1	Transfusion of Nonautologous Cord Blood Stem Cells into Central Artery, Percutaneous Approach
30263Y0	Transfusion of Autologous Hematopoietic Stem Cells into Central Artery, Percutaneous Approach
30263Y1	Transfusion of Nonautologous Hematopoietic Stem Cells into Central Artery, Percutaneous Approach
3E03305	Introduction of Other Antineoplastic into Peripheral Vein, Percutaneous Approach
3E04305	Introduction of Other Antineoplastic into Central Vein, Percutaneous Approach
3E05305	Introduction of Other Antineoplastic into Peripheral Artery, Percutaneous Approach
3E06305	Introduction of Other Antineoplastic into Central Artery, Percutaneous Approach

Description

ACUTE MYELOID LEUKEMIA

Acute myeloid leukemia (AML), also called acute nonlymphocytic leukemia, AML 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 21,380 new cases are diagnosed annually.[1]

Pathophysiology

The pathogenesis of AML is unclear. It can be subdivided by similarity to different subtypes of normal myeloid precursors using the French-American-British classification system. This system classifies leukemias from M0 to M7, based on morphology and cytochemical staining, with immunophenotypic data in some instances. The World Health Organization 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.

Classification
The World Health Organization system recognizes 5 major subcategories of AML: (1) AML with recurrent genetic abnormalities; (2) AML with multilineage dysplasia; (3) therapy-related AML and myelodysplasia; (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), inv16 (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 inv16 or t(16;16). AML patients with 11q23 translocations include 2 subgroups: AML in infants and therapy-related leukemia. Multilineage dysplasia AML must exhibit dysplasia in 50% or more of the cells of 2 or more lineages, which is associated with cytogenetic findings that include --5, 5q-, -7, 7q-, +8, +9, +11, 11q-, 12p-, -18, +19, 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 French-American-British classification, except for the definition of AML as having a minimum of 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.

Genetic Abnormalities
Molecular studies have identified a number of genetic abnormalities that also can be used to guide prognosis and management of AML. Cytogenetically normal 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 variants that affect outcomes, six of which have been identified. The *FLT3* gene that encodes FMS-like receptor tyrosine kinase 3, a growth factor active in hematopoiesis, is mutated in 33% to 49% of cytogenetically normal AML cases; among those, 28% to 33% consist of internal tandem duplications, 5% to 14% are missense variants in exon 20 of the tyrosine kinase activation loop, and the rest are single nucleotide variants (SNVs) in the juxtamembrane domain. All *FLT3* variants result in a constitutively activated protein and confer a poor prognosis. Several pharmaceutic agents that inhibit the *FLT3* tyrosine kinase are under investigation.

Treatment
Complete remission can be achieved initially using induction therapy, consisting of conventional doses of combination chemotherapy. A complete response is achieved in 60% to 80% of adults younger than 60 years of age and in 40% to 60% in patients older than 60 years of age. However, the high incidence of disease relapse has prompted research into a variety of postremission (consolidation) strategies, typically using high-dose chemotherapy with autologous hematopoietic cell transplantation (HCT) or high-dose or reduced-intensity chemotherapy with allogeneic HCT (allo-HCT). The 2 treatments-autologous HCT and allo-HCT-represent 2 different strategies. The first, autologous HCT, is a “rescue,” but not a therapeutic procedure; the second, allo-HCT, is a “rescue” plus a therapeutic procedure.

Hematopoietic Cell Transplantation
HCT is a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allo-HCT). 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 “naive” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD). Cord blood is discussed in policy #285.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT; however, immunologic compatibility between donor and patient is critical for achieving a good outcome with allo-HCT. Immunologic compatibility is established by classifying human leukocyte antigens (HLAs) 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 (with the exception of umbilical cord blood).

Conventional Conditioning for HCT
The conventional practice of allo-HCT involves administration of cytotoxic agents (eg, cyclophosphamide, busulfan) with or without total body irradiation; this is performed at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect of this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that is mediated by non-self-immunologic effector cells that develop after engraftment of allogeneic stem cells within the patient's bone marrow space. While the slower GVM effect is considered 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 medically fit to tolerate substantial adverse events that include preengraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allo-HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increase susceptibility to opportunistic infections. The immune reactivity between donor T cells and malignant cells is responsible for the GVM effect; it also leads to acute and chronic GVHD.

The success of autologous HCT 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 before undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed when the patient's disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

Reduced-Intensity Conditioning for Allo-HCT
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 2-fold: to reduce disease burden, and to minimize treatment-related morbidity and nonrelapse mortality when 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 nonrelapse mortality and relapse due to residual disease. RIC regimens can be viewed as a continuum—from nearly totally myeloablative to minimally myeloablative with lymphoablation—because it tailors its intensity to specific diseases and patient condition. Patients who undergo RIC with allo-HCT 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 this evidence review, RIC refers to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

A 2015 review in the *New England Journal of Medicine* has summarized recent advances in the classification of AML, the genomics of AML and prognostic factors, and current and new treatments.

Summary

For individuals who have cytogenetic or molecular intermediate- or poor-risk AML in first complete remission who receive allo-HCT with myeloablative conditioning (MAC), the evidence includes randomized controlled trials and matched cohort studies. Relevant outcomes are overall survival and disease-specific survival. The evidence has revealed that allo-HCT is better at improving overall and disease-specific survival rates in patients with AML in first complete remission than conventional chemotherapy. All trials employed natural randomization based on donor availability and an intention-to-

treat analysis. Survival rates appear to be associated with the presence of minimal residual disease and risk category. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have AML refractory to standard induction chemotherapy who receive allo-HCT with MAC, the evidence includes retrospective data compiled from patients entered in phase 3 trials and registry data. Relevant outcomes are overall survival and disease-specific survival. The evidence would suggest that allo-HCT improves overall and disease-specific survival rates in patients who are refractory to induction chemotherapy better than conventional chemotherapy. While there are some limitations to the evidence, which include its retrospective nature, lack of rigorous randomization, and general pitfalls of registry data, these results may provide clinically meaningful benefit for patients who do not have other treatment options. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have AML who relapsed after standard induction chemotherapy-induced first complete remission who receive allo-HCT or autologous HCT with MAC, the evidence includes retrospective data compiled from patients entered in phase 3 trials and registry data. Relevant outcomes are overall survival and disease-specific survival. The evidence has shown that allo-HCT improves overall survival rates in patients with relapsed AML better than conventional chemotherapy. Limitations of the evidence include its retrospective nature, lack of rigorous randomization, and pitfalls of registry data. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have cytogenetic or molecular intermediate- or poor-risk AML in first complete remission and for medical reasons cannot tolerate MAC who receive allo-HCT with reduced-intensity conditioning, the evidence includes 2 randomized controlled trials, 2 meta-analyses, and other comparative and noncomparative studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity. The randomized controlled trials compared reduced-intensity conditioning with MAC and reported similar rates in nonrelapse mortality, relapse, and overall survival though one of the trials was stopped prematurely due to a slow accrual of patients. Two retrospective comparative studies found no difference in overall survival or leukemia-free survival between the conditioning regimens. It appears unlikely that additional comparative evidence will be generated. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have AML in first complete remission or beyond without a suitable allo-HCT donor who receive autologous HCT, the evidence includes prospective cohort studies in which patients with an available sibling donor were offered allo-HCT (biologic randomization) with random assignment of all others to autologous HCT or chemotherapy (or no further treatment); and randomized trials comparing autologous HCT with chemotherapy in all patients. Relevant outcomes are overall and disease-specific survival. Compared with chemotherapy, patients undergoing autologous HCT experienced reduced relapse and improved disease-free survival rates. Overall survival did not differ between the groups. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Policy History

Date	Action
10/2018	BCBSA National medical policy review. No changes to policy statements. New references added. Summary clarified.
2/2018	New references added from BCBSA National medical policy. Policy title clarified.
2/2018	Clarified coding information.
3/2016	New references added from BCBSA National medical policy.
10/2015	BCBSA National medical policy review.

	Policy statements updated with clarifying information and to align with other HSCT policies but the intent remains unchanged. 10/1/2015
4/2015	Clarified coding information.
10/2014	New references added from BCBSA National medical policy.
6/2014	Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.
12/2013	New references from BCBSA National medical policy.
12/2012	Updated to add new CPT code 38243
11/2011-4/2012	Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.
7/2011	Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements.
9/2010	Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements.
9/1/2009	New policy, effective 9/1/2009, describing covered and non-covered indications.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References

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