Allogeneic Stem-Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Description of Procedure or Service

Myelodysplastic syndromes and myeloproliferative neoplasms refer to a heterogeneous group of clonal hematopoietic disorders with the potential to transform into acute myelocytic leukemia. Allogeneic hematopoietic stem-cell transplantation (HSCT) has been proposed as a curative treatment option for patients with these disorders.

Hematopoietic Stem-Cell Transplantation

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 of 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.

Reduced-Intensity Conditioning for Allogeneic HCT
Allogeneic Stem-Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

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 lymphoablution, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic 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 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.

Myelodysplastic Syndromes

Myelodysplastic syndromes (MDS) can occur as a primary (idiopathic) disease, or be secondary to cytotoxic therapy, ionizing radiation, or other environmental insult. Chromosomal abnormalities are seen in 40%–60% of patients, frequently involving deletions of chromosome 5 or 7, or an extra chromosome as in trisomy 8. Signs and symptoms of anemia, often complicated by infections or bleeding, are common in MDS; some patients exhibit systemic symptoms or features of autoimmunity that may be indicative of their disease pathogenesis. The vast majority of MDS diagnoses occur in individuals over the age of 55–60 years, with an age-adjusted incidence of about 62% among individuals over age 70 years. Patients either succumb to disease progression to AML or to complications of pancytopenias. Patients with higher blast counts or complex cytogenetic abnormalities have a greater likelihood of progressing to AML than do other patients.

The French-American-British (FAB) system has been used to classify MDS into 5 subtypes as follows: 1) refractory anemia (RA); 2) refractory anemia with ringed sideroblasts (RARS); 3) refractory anemia with excess blasts (RAEB); 4) refractory anemia with excess blasts in transformation (RAEBT); and, 5) chronic myelomonocytic leukemia (CMML). The FAB system has been supplanted by that of the World Health Organization (WHO), which records the number of lineages in which dysplasia is seen (unilineage versus multilineage), separates the 5q- syndrome, and reduces the threshold maximum blast percentage for the diagnosis of MDS from 30% to 20% (see Policy Guidelines for WHO classification scheme for myeloid neoplasms).

The most commonly used prognostic scoring system for MDS is the International Prognostic Scoring System (IPSS). The IPSS groups patients into one of four prognostic categories based on the number of cytopenias, cytogenetic profile and the percentage blasts in the bone marrow (see Policy Guidelines). This system underweights the clinical importance of severe, life-threatening neutropenia and thrombocytopenia in therapeutic decisions and does not account for the rate of change in critical parameters, such as peripheral blood counts or blast percentage. However, the IPSS has been useful in comparative analysis of clinical trial results and its utility confirmed at many institutions. An updated 5-category IPSS has been proposed for prognosis in patients with primary MDS or secondary AML to account for chromosomal abnormalities frequently seen in MDS. This system stratifies patients into 5 categories: very poor, poor intermediate, good and very good. There has been investigation into using the 5-category IPSS to better characterize risk in MDS. A second prognostic scoring system incorporates the WHO subgroup classification that accounts for blast percentage, cytogenetics, and severity of cytopenias as assessed by transfusion requirements. The WPSS uses a 6-category system which allows more precise prognostication of overall survival duration as well as risk for progression to AML. This system, however, is not yet in widespread use in clinical trials.
Allogeneic Stem-Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Treatment of smoldering or nonprogressing MDS has in the past involved best supportive care including red blood cell (RBC) and platelet transfusions and antibiotics. Active therapy was given only when MDS progressed to AML or resembled AML with severe cytopenias. A diverse array of therapies are now available to treat MDS, including hematopoietic growth factors (e.g., erythropoietin, darbepoetin, granulocyte colony-stimulating factor), transcriptional-modifying therapy (e.g., U.S. Food and Drug Administration-approved hypomethylating agents, nonapproved histone deacetylase inhibitors), immunomodulators (e.g., lenalidomide, thalidomide, antithymocyte globulin, cyclosporine A), low-dose chemotherapy (e.g., cytarabine), and allogeneic HCT. Given the spectrum of treatments available, the goal of therapy must be decided upfront, whether it is to improve anemia, thrombocytopenia, or neutropenia; eliminate the need for RBC transfusion; achieve complete remission (CR); or, cure the disease. Allogeneic HSCT is the only approach with curative potential, but its use is governed by patient age, performance status, medical comorbidities, the patient’s risk preference, and severity of MDS at presentation.

Chronic Myeloproliferative Neoplasms

Chronic myeloproliferative neoplasms (MPN) are clonal bone marrow stem cell disorders; as a group, approximately 8400 MPN are diagnosed annually in the United States. Like MDS, MPN primarily occur in older individuals, with approximately 67% reported in patients aged 60 years and older. MPNs are characterized by the slow but relentless expansion of a clone of cells with the potential evolution into a blast crisis similar to AML. MPN share a common stem cell–derived clonal heritage, with phenotypic diversity attributed to abnormal variations in signal transduction as the result of a spectrum of mutations that affect protein tyrosine kinases or related molecules. The unifying characteristic common to all MPN is effective clonal myeloproliferation resulting in peripheral granulocytosis, thrombocytosis, or erythrocytosis that is devoid of dyserythropoiesis, granulocytic dysplasia, or monocytosis.

In 2008, a new WHO classification scheme replaced the term chronic myeloproliferative disorder (CMPD) with the term myeloproliferative neoplasms (MPN). These are a subdivision of myeloid neoplasms that includes the four classic disorders chronic myeloid leukemia (CML), polycythemia vera (PCV), essential thrombocythemia (ET), and primary myelofibrosis (PMF); the WHO classification also includes chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia/hypereosinophilic syndrome (CEL/HES), mast cell disease (MCD), and MPNs unclassifiable (see Policy Guidelines).

In indolent, nonprogressing cases, therapeutic approaches are based on relief of symptoms. Supportive therapy may include prevention of thromboembolic events. Hydroxyurea may be used in cases of high-risk essential thrombocytosis and polycythemia vera, and intermediate- and high-risk primary myelofibrosis.

In November 2011, FDA approved the orally administered selective Janus kinase 1 and 2 inhibitor ruxolitinib for the treatment of intermediate- or high-risk myelofibrosis. Ruxolitinib has been associated with improved OS, spleen size, and symptoms of myelofibrosis when compared with placebo. The COMFORT-II trial compared ruxolitinib to best available therapy in patients with intermediate- and highrisk myelofibrosis, and demonstrated improvements in spleen volume and OS. In a randomized trial comparing ruxolitinib to best available therapy, including antineoplastic agents, most commonly hydroxyurea, glucocorticoids, and no therapy, for myelofibrosis, Harrison et al demonstrated improvements in spleen size and quality of life, but not OS.

Myeloablative allo-HCT has been considered the only potentially curative therapy, but because most patients are of advanced age with attendant comorbidities, its use is limited to those who can tolerate the often severe treatment-related adverse effects of this procedure. However, use of RIC of conditioning regimens for allo-HCT has extended the potential benefits of this procedure to selected individuals with these disorders.
Allogeneic Stem-Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Related Policies:
Hematopoietic Stem-Cell Transplantation for Acute Myeloid Leukemia
Hematopoietic Stem-Cell Transplantation for Chronic Myelogenous Leukemia

***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 allogeneic hematopoietic stem-cell transplantation for myelodysplastic syndromes or myeloproliferative neoplasms when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

BCBSNC will provide coverage for reduced-intensity conditioning allogeneic hematopoietic stem-cell transplantation for myelodysplastic syndromes or myeloproliferative neoplasms 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.

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 Allogeneic Stem-Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms are covered

Allogeneic hematopoietic stem-cell transplantation (HSCT) may be considered medically necessary as a treatment of:

- myelodysplastic syndromes (see Policy Guidelines) or
- myeloproliferative neoplasms (see Policy Guidelines).

Reduced-intensity conditioning allogeneic HSCT may be considered medically necessary for patients who for medical reasons would be unable to tolerate a myeloablative conditioning regime as a treatment of:

- myelodysplastic syndromes (see Policy Guidelines); or
- myeloproliferative neoplasms (see Policy Guidelines).
Allogeneic Stem-Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

When Allogeneic Stem-Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms are not covered

Allogeneic hematopoietic stem-cell transplantation for myelodysplastic syndromes or myeloproliferative neoplasms that do not meet the criteria and guidelines are considered not medically necessary.

Policy Guidelines

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

For individuals who have MDS and MPN who receive myeloablative conditioning allo-HCT, the evidence includes case series, which are often heterogeneous in terms of diseases included. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. Primarily uncontrolled, observational studies of HCT for MDS report a relatively large range of overall and progression-free survival values, which reflects the heterogeneity in patient populations, conditioning regimens, and other factors. Reported estimates for 3- to 5-year overall survival of approximately 40% to 50% are typical. For HSCT for MPN, data are more limited. At least 1 comparative study of HCT for myelofibrosis demonstrated improved survival with HCT compared with standard therapy. HCT is at present the only potentially curative treatment option for patients with MDS and MPN. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have MDS and MPN who receive reduced-intensity conditioning allo-HCT, the evidence includes primarily retrospective observational series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. Direct, prospective comparisons of outcomes after HCT with either myeloablative conditioning or RIC in either MDS or MPN are not available. Evidence from retrospective nonrandomized comparisons suggests that RIC may be used in patients who are older and with more comorbidities without significantly worsening overall survival. RIC appears to be associated with lower rates of nonrelapse mortality but higher cancer relapse than myeloablative HCT. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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, 38230, 38240, 38242,38243, 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
Allogeneic Stem-Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms


Policy Implementation/Update Information

2/01 Original policy issued.
2/03 Specialty Matched Consultant Advisory Panel review 11/2002. Revised statement under when it is covered to include, "HDC with HLA matched sibling stem cell support may be considered medically necessary as a treatment of myelodysplastic syndromes based on International Prognostic Scoring System (IPSS) for myelodysplastic syndromes and National Comprehensive Cancer Network (NCCN) practice guidelines. Guidelines are available at
Allogeneic Stem-Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

http://www.nccn.org/physician_gls/f_guidelines.html (see Myelodysplastic Syndromes). Revised under Policy Guidelines section to include, "HDC and allogeneic stem cell support should be administered through a clinical trial whenever possible." Codes 86812-86822 removed; codes 38231 and 86915 deleted and codes 38242 and 38205 added to the Billing/Coding section. System coding changes.

3/03 Format changes. Removed hyperlink for the term "allogeneic" in the Policy Implementation/Update Information section. Revised the website for NCCN in the Scientific Background and Reference Sources section.

1/04 Benefits Application and Billing/Coding sections updated for consistency.

7/29/04 HCPCS code S2150 added to Billing/Coding section.

12/9/04 Specialty Matched Consultant Advisory Panel review 11/29/04. Description of Procedure or Service revised. Added additional Policy statement to include myeloproliferative disorders. Additional indication added under When Allogeneic Bone Marrow Transplant for Myelodysplastic Diseases are Covered section. "B. 3. Essential thrombocythemia with an associated thrombotic or hemorrhagic disorder". Added information to Policy Guidelines section. Added policy number to Policy Key Words section. References added.


6/22/10 Policy Number(s) removed. (amw)

7/6/10 Policy name changed from Bone Marrow Transplant Allogeneic for Myelodysplastic Diseases. Policy status changed from "Active policy, no longer scheduled for routine literature review." to active policy. "Description" section extensively revised. References to "High-dose chemotherapy with stem-cell support" changed to Hematopoietic stem-cell transplantation throughout the policy as appropriate. No change to policy statement. "Policy Guidelines" updated and expanded. Specialty Matched Consultant Advisory Panel review 5/24/2010. References added. (btw)


2/7/12 Reference added. (btw)

5/15/12 Specialty Matched Consultant Advisory Panel review 4/18/2012. No change to policy intent. Policy Guidelines updated. (btw)

1/15/12 Added new 2013 CPT code, 38243, to Billing/Coding section. Reference added. (btw)

4/30/13 Specialty Matched Consultant Advisory Panel review 4/17/2013. No change to policy. (btw)

2/11/14 Description and Policy Guidelines sections updated. No change to policy intent. Reference added. (btw)


1/13/15 Reference added. (lpr)

5/26/15 Specialty Matched Consultant Advisory Panel review 4/29/2015. No change to policy. (lpr)

5/31/16 Updated Description and Policy Guidelines sections. Reference added. Specialty Matched Consultant Advisory Panel review 4/27/2016. No change to policy statement. (lpr)

2/24/17 Revised Policy Guidelines section. Reference added. No change to policy statement. (lpr)
Allogeneic Stem-Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

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.