



BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Allogeneic Stem-Cell Transplantation of Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Policy # 00061

Original Effective Date: 01/28/2002

Current Effective Date: 12/18/2013

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member's contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider allogeneic hematopoietic stem-cell transplantation (HSCT) as a treatment of myelodysplastic syndrome (MDS) to be **eligible for coverage** when the patient selection criteria are met.

Patient Selection Criteria

Allogeneic hematopoietic stem-cell transplantation (HSCT) as a treatment of myelodysplastic syndrome (MDS) will be considered when any of the following criteria are met:

- Refractory anemia (RA); or
- Refractory anemia with ring sideroblasts (RARS); or
- Refractory cytopenia with multilineage dysplasia (RCMD); or
- Refractory cytopenia with multilineage dysplasia (RCMD) with ring sideroblast; or
- Refractory anemia with excess blasts 1 and 2 (RAEB 1 and 2); or
- Del 5q syndrome; or
- Unclassified myelodysplastic syndrome (MDS).

Based on review of available data, the Company may consider allogeneic hematopoietic stem-cell transplantation (HSCT) as a treatment of myeloproliferative neoplasms (MPNs) to be **eligible for coverage** when the patient selection criteria are met.

Patient Selection Criteria

Allogeneic hematopoietic stem-cell transplantation (HSCT) as a treatment of myeloproliferative neoplasms (MPNs) will be considered when any of the following criteria are met:

- Chronic myelogenous leukemia (CML); or
- Polycythemia vera (PCV); or
- Essential thrombocythemia (ET); or
- Primary myelofibrosis (PMF); or
- Chronic neutrophilic leukemia (CNL); or
- Chronic eosinophilic leukemia (CEL), not otherwise categorized; or
- Hypereosinophilic leukemia; or
- Mast cell disease (MCD); or
- Myeloproliferative neoplasms (MPNs), unclassifiable.

©2013 Blue Cross and Blue Shield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Allogeneic Stem-Cell Transplantation of Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Policy # 00061

Original Effective Date: 01/28/2002

Current Effective Date: 12/18/2013

Based on review of available data, the Company may consider allogeneic hematopoietic stem-cell transplantation (HSCT) as a treatment of both myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPNs) to be **eligible for coverage** when the patient selection criteria are met.

Patient Selection Criteria

Allogeneic hematopoietic stem-cell transplantation (HSCT) as a treatment of both myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPNs) will be considered when any of the following criteria are met:

- Chronic myelomonocytic leukemia (CMML); or
- Juvenile myelomonocytic leukemia; or
- Atypical chronic myeloid leukemia; or
- Myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN), unclassifiable.

Based on review of available data, the Company may consider reduced-intensity conditioning (RIC) allogeneic hematopoietic stem-cell transplantation (HSCT) as a treatment of myelodysplastic syndrome (MDS) or myeloproliferative neoplasms (MPNs) in patients who for medical reasons would be unable to tolerate a myeloablative conditioning regimen to be **eligible for coverage**.

Based on review of available data, the Company may consider allogeneic hematopoietic stem-cell transplantation (HSCT) as a treatment of myeloid neoplasms associated with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1 to be **eligible for coverage** when the patient selection criteria are met.

Patient Selection Criteria

Allogeneic hematopoietic stem-cell transplantation (HSCT) as a treatment of myeloid neoplasms associated with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1 will be considered when ANY of the following criteria are met:

- Myeloid neoplasms associate with PDGFRA rearrangement; OR
- Myeloid neoplasms associate with PDGFRB rearrangement; OR
- Myeloid neoplasms associate with FGFR1 rearrangement (8p11 myeloproliferative syndrome).

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers allogeneic hematopoietic stem-cell transplantation (HSCT) as a treatment of myelodysplastic syndrome (MDS) and/or myeloproliferative neoplasms (MPNs) when patient selection criteria are not met to be **investigational***.

Background/Overview

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



BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Allogeneic Stem-Cell Transplantation of Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Policy # 00061

Original Effective Date: 01/28/2002

Current Effective Date: 12/18/2013

Hematopoietic Stem-Cell Transplantation

Hematopoietic stem-cell transplantation 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 of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. Human leukocyte antigens 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 Hematopoietic Stem-Cell Transplantation

The conventional (“classical”) practice of allogeneic HSCT involves administration of cytotoxic agents (e.g., cyclophosphamide [Cy], busulfan) with or without total body irradiation (TBI) 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 Hematopoietic Stem-Cell Transplantation

Reduced-intensity conditioning 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. Reduced-intensity conditioning 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



BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Allogeneic Stem-Cell Transplantation of Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Policy # 00061
Original Effective Date: 01/28/2002
Current Effective Date: 12/18/2013

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 refer to a heterogeneous group of clonal hematopoietic disorders characterized by impaired maturation of hematopoietic cells and a tendency to transform into AML. Myelodysplastic syndromes can occur as a primary (idiopathic) disease or can 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 older than age 55–60 years, with an age-adjusted incidence of approximately 62% among individuals older than 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.

For the past 20 years, the French-American-British (FAB) system has been used to classify MDS into 5 subtypes as follows: 1) RA; 2) RARS; 3) RAEB; 4) refractory anemia with excess blasts in transformation (RAEBT); and, 5) CMML. However, 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 vs. multilineage), separates the 5q- syndrome, and reduces the threshold maximum blast percentage for the diagnosis of MDS from 30% to 20%

Several prognostic scoring systems for MDS have been proposed; the most commonly used 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 of blasts in the bone marrow. 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. 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 WHO Classification-based Prognostic scoring system (WPSS) uses a 6-category system, which allows more precise prognostication of overall survival (OS) duration, as well as risk for progression to AML. This system, however, is not yet in widespread use in clinical trials.

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),

©2013 Blue Cross and Blue Shield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Allogeneic Stem-Cell Transplantation of Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Policy # 00061
Original Effective Date: 01/28/2002
Current Effective Date: 12/18/2013

immunomodulators (e.g., lenalidomide, thalidomide, antithymocyte globulin, cyclosporine A [CYA]), low-dose chemotherapy (e.g., cytarabine), and allogeneic HSCT. 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

In 2008, a new WHO classification scheme replaced the term chronic myeloproliferative disorder (CMPD) with the term MPNs. These are a subdivision of myeloid neoplasms that includes the four classic disorders: CML, PCV, ET, and PMF; the WHO classification also includes CNL, CEL/hypereosinophilic syndrome (HES), MCD, and MPNs unclassifiable.

The 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. They 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 MPNs is effective clonal myeloproliferation resulting in peripheral granulocytosis, thrombocytosis, or erythrocytosis that is devoid of dyserythropoiesis, granulocytic dysplasia, or monocytosis.

As a group, approximately 8,400 MPNs are diagnosed annually in the U.S. Like MDS, MPNs primarily occur in older individuals, with approximately 67% reported in patients aged 60 years and older. In indolent, nonprogressing cases, therapeutic approaches are based on relief of symptoms. Myeloablative (MA) allogeneic HSCT 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, the use of RIC of conditioning regimens for allogeneic HSCT has extended the potential benefits of this procedure to selected individuals with these disorders.

Rationale/Source

Myelodysplastic Syndromes

Despite the successes seen with new drugs now available to treat MDS (e.g., decitabine, azacitidine, lenalidomide), allogeneic HSCT is the only treatment capable of complete and permanent eradication of the MDS clone. A review of allogeneic HSCT using myeloablative conditioning for MDS included 24 studies (prospective and retrospective) published between 2000 and 2008 that included a total 1,378 cases with age range of 32–59 years. A majority of patients (n = 885) received matched related donor (MRD) allogeneic HSCT, with other donor types including syngeneic, matched, unrelated donor (MUD), mismatched unrelated donor (URD), and umbilical cord blood. Most studies included de novo and secondary MDS, CMML, MPNs, de novo and secondary AML and transformed AML. Peripheral blood and bone marrow stem-cell grafts were allowed in most studies. The most commonly used conditioning regimens were busulfan plus cyclophosphamide (BU/CY) and CY plus total body irradiation (CY/TBI), with CYA used for GVHD prophylaxis. Length of follow-up ranged from 5 months to approximately 8 years.

©2013 Blue Cross and Blue Shield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Allogeneic Stem-Cell Transplantation of Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Policy # 00061
Original Effective Date: 01/28/2002
Current Effective Date: 12/18/2013

Grades II-IV acute GVHD varied from 18% to 100%. Relapse risk ranged from a low of 24% at 1 year to 36% at 5 years. Overall survival ranged from 25% at 2 years to 52% at 4 years, with NRM ranging from 19% at day 100 to 61% at 5 years.

Evidence from a number of largely heterogeneous, uncontrolled studies of RIC with allogeneic HSCT shows long-term remissions (i.e., longer than 4 years) can be achieved, often with reduced treatment-related morbidity and mortality, in patients with MDS/AML who otherwise would not be candidates for MA conditioning regimens. These prospective and retrospective studies included cohorts of 16–215 patients similar to those in the MA allogeneic HSCT studies. The most common conditioning regimens used were fludarabine-based, with CYA and tacrolimus used for GVHD prophylaxis. The reported incidence of grades II–IV GVHD was 9–63%, with relapse risk of 6–61%. The OS rates ranged between 44% at 1 year to 46% at 5 years, with a median follow-up range of 14 months to over 4 years.

In 2013, Kim and colleagues published a randomized Phase III trial to compare the toxicities of 2 different conditioning regimens (reduced cyclophosphamide [Cy], fludarabine, and anti-thymocyte globulin [ATG]; standard Cy-ATG). Four (of 83) patients had MDS, and the remaining study patients had severe aplastic anemia. Overall, the incidence of toxicities were reported to be lower in patients receiving the reduced-conditioning regimen (23% vs. 55%; $p = 0.003$). Subgroup analyses showed no differences in the overall results based on differential diagnosis.

In general, these RIC trials showed a low rate of engraftment failure and low NRM, but at the cost of a higher relapse rate than with myeloablative allogeneic HSCT. However, in the absence of prospective, comparative, randomized trials, only indirect comparisons can be made between the relative clinical benefits and harms associated with myeloablative and RIC regimens with allogeneic HSCT. Furthermore, no randomized trials have been published in which RIC with allogeneic HSCT has been compared with conventional chemotherapy alone, which has been the standard of care in patients with MDS/AML for whom myeloablative chemotherapy and allogeneic HSCT are contraindicated. Nonetheless, given the absence of curative therapies for these patients, RIC allogeneic HSCT may be considered medically necessary for patients with MDS who could benefit from allogeneic HSCT but who for medical reasons would be unable to tolerate a myeloablative conditioning regimen.

The recommendations of a systematic review of the role of allogeneic HSCT in patients with MDS prepared by the American Society for Blood and Marrow Transplantation (ASBMT) are congruent with the present policy statements. Other recent reviews concur with the ASBMT recommendations.

Myeloproliferative Neoplasms

Data on therapy for MPN remain sparse. As outlined previously in this policy, with the exception of myeloablative chemotherapy and allogeneic HSCT, no therapy has yet been proven to be curative or to prolong survival of patients with MPN. However, the significant toxicity of myeloablative conditioning and allogeneic HSCT in MPN has led to study of RIC regimens for these diseases. One recent series included 27 patients (mean age: 59 years) with MPN who underwent allogeneic HSCT using a RIC regimen of low-dose (2 Gy) TBI alone or with the addition of fludarabine. At a median follow-up of 47 months, the 3-year relapse-free survival (RFS) was 37% and OS was 43%, with a 3-year nonrelapse mortality of 32%. In a



BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Allogeneic Stem-Cell Transplantation of Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Policy # 00061

Original Effective Date: 01/28/2002

Current Effective Date: 12/18/2013

second series, 103 patients (median age 55 years, range 32-68 years) with intermediate to high risk (86% of total patients) PMF or post-essential thrombocythemia (PT) and polycythemia vera myelofibrosis (PVM) were included on a prospective multicenter Phase II trial to determine efficacy of a busulfan plus fludarabine-based RIC regimen followed by allogeneic HSCT from related (n = 33) or unrelated (n = 70) donors. Acute grade II-IV GVHD occurred in 27%, and chronic GVHD in 43% of patients. The cumulative incidence of NRM at 1 year in all patients was 16% (95% confidence interval [CI], 9-23%) but reached 38% (95% CI, 15-61%) among those with a mismatched donor versus 12% (95% CI, 5-19%) among cases with a matched donor (p = 0.003). The cumulative relapse rate at 3 and 5 years was 22% (95% CI, 13-31%) and 29% (95% CI, 16-42%), respectively. After a median follow-up of 33 months (range, 12-76 months) 5-year estimated disease-free survival (DFS) and OS was 51% (95% CI, 38-64%) and 67% (95% CI, 55-79%), respectively.

The largest study of allogeneic HSCT for PMF comes from analysis of the outcomes of 289 patients treated between 1989 and 2002, from the database of the Center for International Bone Marrow Transplant Research (CIBMTR). The median age was 47 years (range: 18-73 years). Donors were HLA-identical siblings in 162 patients, unrelated individuals in 101 patients, and HLA nonidentical family members in 26 patients. Patients were treated with a variety of conditioning regimens and GVHD prophylaxis regimens. Splenectomy was performed in 65 patients prior to transplantation. The 100-day treatment-related mortality was 18% for HLA identical sibling transplants, 35% for unrelated transplants, and 19% for transplants from alternative related donors. Corresponding 5-year OS rates were 37%, 30%, and 40%, respectively. Disease-free survival rates were 33%, 27%, and 22%, respectively. Disease-free survival for patients receiving reduced-intensity transplants was comparable: 39% for HLA identical sibling donors and 17% for unrelated donors at 3 years. In this large retrospective series, allogeneic transplantation for myelofibrosis (MF) resulted in long-term RFS in about one-third of patients.

Data from direct, prospective comparison of outcomes of myeloablative conditioning and allogeneic HSCT versus RIC and allogeneic stem-cell support in MPN are not available. However, a recent retrospective study analyzed the impact of conditioning intensity on outcomes of allogeneic HSCT in patients with MF. This multicenter trial included 46 consecutive patients treated at 3 Canadian and 4 European transplant centers between 1998 and 2005. Twenty-three patients (median age 47 years, range 31-60 years) underwent myeloablative conditioning, and 23 patients (median age 54 years, range 38-74 years) underwent RIC. The majority in both groups (85%) were deemed intermediate- or high-risk. At a median follow-up of 50 (range 20-89) months, there was a trend for better progression-free survival (PFS) at 3 years in RIC patients compared to myeloablative-conditioned patients (58%, range 23-62 vs. 43%, range 35-76, respectively, p = 0.11); there was a similar trend in 3-year OS (68%, range 45-84 vs. 48%, range 27-66, respectively, p = 0.08). Non-relapse mortality rates at 3 years trended higher in myeloablative conditioned cases than RIC cases (48%, range 31-74 vs. 27%, range 14-55, respectively, p = 0.08). The results of this study suggest that both types of conditioning regimens have curative potential in patients with MF. Despite the RIC patients being significantly older with longer disease duration and poorer performance status than those who received conventional conditioning, the groups had similar outcomes, supporting the use of RIC allogeneic HSCT in this population.

©2013 Blue Cross and Blue Shield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Allogeneic Stem-Cell Transplantation of Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Policy # 00061
Original Effective Date: 01/28/2002
Current Effective Date: 12/18/2013

In a retrospective study in 9 Nordic transplant centers, a total of 92 patients with MF in chronic phase underwent allogeneic HSCT. MA-conditioning was given to 40 patients, and RIC was used in 52 patients. The mean age in the 2 groups at transplantation was 46 ± 12 and 55 ± 8 years, respectively ($p < 0.001$). When adjustment for age differences was made, the survival of the patients treated with RIC was significantly better ($p = 0.003$). Among the RIC patients, survival was significantly ($p = 0.003$) greater for patients younger than age 60 years (a 10-year survival close to 80%) than for patients older than 60 years. The stem-cell source did not significantly affect the survival. No significant difference was found in NRM at 100 days between the MA- and the RIC-treated patients. The probability of survival at 5 years was 49% for the MA-treated patients and 59% in the RIC group ($p = 0.125$). Patients treated with RIC experienced significantly less acute GVHD compared with patients treated with MA conditioning ($p < 0.001$). The OS at 5 years was 70%, 59% and 41% for patients with Lille score 0, 1 and 2, respectively ($p = 0.038$, when age adjustment was made). Twenty-one percent of the patients in the RIC group were given donor lymphocyte infusion because of incomplete donor chimerism, compared with none of the MA-treated patients ($p < 0.002$). Nine percent of the patients needed a second transplant because of graft failure, progressive disease or transformation to AML, with no significant difference between the groups.

Ongoing Clinical Trials

A search of the National Cancer Institute (NCI) Clinical Trials Database in October 2013 identified 8 active Phase III trials that involve stem-cell support for patients with MDS/AML or MPN. Information on these trials can be accessed via the following link, available online at: <http://www.cancer.gov/clinicaltrials/search/results?protocolsearchid=9718439>. In addition, a search of online site ClinicalTrials.gov identified numerous Phase II trials of various treatments for these diseases which are actively recruiting patients.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

In response to requests, input was received from two Academic Medical Center specialists prior to review for May 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 consensus among reviewers that RIC allogeneic HSCT was of value in patients with MDS or MPN who would be medically unable to tolerate a MA HSCT.

Summary

Hematopoietic stem-cell transplantation is at present the only potentially curative treatment option for patients with MDSs and MPNs. The absence of other curative therapies coupled with clinical data and input permit the conclusion that allogeneic HSCT using either a myeloablative or RIC regimen is medically necessary in appropriately selected patients with these conditions. Patient selection is guided by age and disease risk factors.



BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Allogeneic Stem-Cell Transplantation of Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Policy # 00061
Original Effective Date: 01/28/2002
Current Effective Date: 12/18/2013

National Comprehensive Cancer Network Guidelines

The 2014 National Comprehensive Cancer Network (NCCN) treatment guidelines (v.2.2014) for the use of allogeneic HSCT indicate this procedure is preferred at diagnosis in patients who are candidates for high-intensity therapy, have a suitable donor, and have de novo MDS classified as IPSS Int-2 and High, or those who have de novo MDS classified as Int-1 with severe cytopenias unresponsive to standard therapies (available online at: http://www.nccn.org/professionals/physician_gls/pdf/mds.pdf). Reduced-intensity or MA-conditioning may be used based on patient age, performance status, comorbid conditions, psychosocial status, patient preference, and availability of caregiver. Matched related donor cells are preferred, but MUD cells are an option at some centers. The role of pretransplant remission induction using intensive chemotherapy has not been established.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Allogeneic Stem-Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms", 8.01.21, 11:2013.
2. Kasner MT, Luger SM. Update on the therapy for myelodysplastic syndrome. *Am J Hematol* 2009; 84(3):177-86.
3. Barrett AJ, Savani BN. Allogeneic stem cell transplantation for myelodysplastic syndrome. *Semin Hematol* 2008; 45(1):49-59.
4. 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.
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. 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.
7. Kindwall-Keller T, Isola LM. The evolution of hematopoietic SCT in myelodysplastic syndrome. *Bone Marrow Transplant* 2009; 43(8):597-609.
8. Kroger N, Bornhauser M, Ehninger G et al. Allogeneic stem cell transplantation after a fludarabine/busulfan-based reduced-intensity conditioning in patients with myelodysplastic syndrome or secondary acute myeloid leukemia. *Ann Hematol* 2003; 82(6):336-42.
9. Laport GG, Sandmaier BM, Storer BE et al. Reduced-intensity conditioning followed by allogeneic hematopoietic cell transplantation for adult patients with myelodysplastic syndrome and myeloproliferative disorders. *Biol Blood Marrow Transplant* 2008; 14(2):246-55.
10. Martino R, Caballero MD, Perez-Simon JA et al. Evidence for a graft-versus-leukemia effect after allogeneic peripheral blood stem cell transplantation with reduced-intensity conditioning in acute myelogenous leukemia and myelodysplastic syndromes. *Blood* 2002; 100(6):2243-5.
11. Mesa RA. Navigating the evolving paradigms in the diagnosis and treatment of myeloproliferative disorders. *Hematology Am Soc Hematol Educ Program* 2007:355-62.
12. Tauro S, Craddock C, Peggs K et al. Allogeneic stem-cell transplantation using a reduced-intensity conditioning regimen has the capacity to produce durable remissions and long-term disease-free survival in patients with high-risk acute myeloid leukemia and myelodysplasia. *J Clin Oncol* 2005; 23(36):9387-93.
13. 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.
14. 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.
15. Kim H, Lee JH, Joo YD et al. A randomized comparison of cyclophosphamide vs. reduced dose cyclophosphamide plus fludarabine for allogeneic hematopoietic cell transplantation in patients with aplastic anemia and hypoplastic myelodysplastic syndrome. *Ann Hematol* 2012; 91(9):1459- 69.
16. Oliansky DM, Antin JH, Bennett JM et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of myelodysplastic syndromes: an evidence-based review. *Biol Blood Marrow Transplant* 2009; 15(2):137-72.
17. Akhtari M. When to treat myelodysplastic syndromes. *Oncology (Williston Park)* 2011; 25(6):480-6.
18. Deeg HJ, Sandmaier BM. Who is fit for allogeneic transplantation? *Blood* 2010; 116(23):4762-70.



Blue Cross Blue Shield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Allogeneic Stem-Cell Transplantation of Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Policy # 00061
 Original Effective Date: 01/28/2002
 Current Effective Date: 12/18/2013

19. Giralt SA, Horowitz M, Weisdorf D et al. Review of stem-cell transplantation for myelodysplastic syndromes in older patients in the context of the Decision Memo for Allogeneic Hematopoietic Stem Cell Transplantation for Myelodysplastic Syndrome emanating from the Centers for Medicare and Medicaid Services. *J Clin Oncol* 2011; 29(5):566-72.
20. Deeg HJ, Bartenstein M. Allogeneic hematopoietic cell transplantation for myelodysplastic syndrome: current status. *Arch Immunol Ther Exp (Warsz)* 2012; 60(1):31-41.
21. Garcia-Manero G. Myelodysplastic syndromes: 2012 update on diagnosis, risk-stratification, and management. *Am J Hematol* 2012; 87(7):692-701.
22. Kroger N. Allogeneic stem cell transplantation for elderly patients with myelodysplastic syndrome. *Blood* 2012; 119(24):5632-9.
23. Tefferi A, Vainchenker W. Myeloproliferative neoplasms: molecular pathophysiology, essential clinical understanding, and treatment strategies. *J Clin Oncol* 2011; 29(5):573-82.
24. McLornan DP, Mead AJ, Jackson G et al. Allogeneic stem cell transplantation for myelofibrosis in 2012. *Br J Haematol* 2012; 157(4):413-25.
25. Kroger N, Holler E, Kobbe G et al. Allogeneic stem cell transplantation after reduced-intensity conditioning in patients with myelofibrosis: a prospective, multicenter study of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Blood* 2009; 114(26):5264-70.
26. Ballen KK, Shrestha S, Sobocinski KA et al. Outcome of transplantation for myelofibrosis. *Biol Blood Marrow Transplant* 2010; 16(3):358-67.
27. Gupta V, Kroger N, Aschan J et al. A retrospective comparison of conventional intensity conditioning and reduced-intensity conditioning for allogeneic hematopoietic cell transplantation in myelofibrosis. *Bone Marrow Transplant* 2009; 44(5):317-20.
28. Abellsson J, Merup M, Birgegard G et al. The outcome of allo-HSCT for 92 patients with myelofibrosis in the Nordic countries. *Bone Marrow Transplant* 2012; 47(3):380-6.

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2012 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	38204, 38205, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38230, 38240, 38242, 38243
HCPCS	S2140, S2142, S2150
ICD-9 Diagnosis	238.72 thru 238.79
ICD-9 Procedure	41.00, 41.01, 41.02, 41.03, 41.04, 41.05, 41.06, 41.07, 41.08, 41.09, 41.91, 99.79



BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Allogeneic Stem-Cell Transplantation of Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Policy # 00061
Original Effective Date: 01/28/2002
Current Effective Date: 12/18/2013

Policy History

Original Effective Date:	01/28/2002
Current Effective Date:	12/18/2013
01/28/2002	Managed Care Advisory Council approval
06/24/2002	Format revision. No substance change to policy.
07/06/2004	Medical Director review
07/20/2004	Medical Policy Committee review. Format revision. High-Dose Chemotherapy and Hematopoietic Stem Cell Support for Myelodysplastic Diseases and Myeloproliferative Disorders policy developed separately from current HDC with Hematopoietic Stem Cell Support policy. Coverage eligibility unchanged.
07/26/2004	Managed Care Advisory Council approval
05/03/2005	Medical Director review
05/17/2005	Medical Policy Committee review. Coverage eligibility change; "HDC and autologous SCS as initial treatment (i.e., in lieu of an initial course of conventional chemotherapy) of poor-risk germ cell tumors, or as initial treatment of a first relapse (i.e., in lieu of a course of conventional chemotherapy) is investigational".
05/23/2005	Managed Care Advisory Council approval
06/07/2006	Medical Director review
06/21/2006	Medical Policy Committee approval. Format revisions, FDA/Governmental, Rationale/Source. Coverage eligibility unchanged.
05/02/2007	Medical Director review
05/23/2007	Medical Policy Committee approval. No change to coverage eligibility.
10/01/2008	Medical Director review
10/22/2008	Medical Policy Committee approval. No change to coverage eligibility.
12/04/2009	Medical Policy Committee approval
12/16/2009	Medical Policy Implementation Committee approval. Title changed from "Allogeneic Stem Cell Transplantation of Myelodysplastic and Myeloproliferative Diseases" to "Allogeneic Stem Cell Transplantation of Myelodysplastic Syndromes and Myeloproliferative Neoplasms". Added criteria to the coverage for the treatment of myelodysplastic syndromes. Added criteria to the coverage for the treatment of myeloproliferative neoplasms. Added coverage with criteria for treatment of both myelodysplastic syndromes and myeloproliferative neoplasms. Added reduced-intensity conditioning allogeneic hematopoietic stem cell transplantation to be eligible for coverage.
12/01/2010	Medical Policy Committee review
12/15/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/08/2011	Medical Policy Committee review
12/21/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/06/2012	Medical Policy Committee review
12/19/2012	Medical Policy Implementation Committee approval. Added coverage with criteria for allogeneic hematopoietic stem-cell transplantation as a treatment of myeloid neoplasms associated with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1.
03/04/2013	Coding updated
12/12/2013	Medical Policy Committee review
12/18/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date:	12/2014

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

©2013 Blue Cross and Blue Shield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Allogeneic Stem-Cell Transplantation of Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Policy # 00061

Original Effective Date: 01/28/2002

Current Effective Date: 12/18/2013

- A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 - 2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. reference to federal regulations.

****Medically Necessary (or "Medical Necessity")** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. in accordance with nationally accepted standards of medical practice;
- B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.