



# BlueCross BlueShield of Louisiana

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## Allogeneic Stem-Cell Transplantation of Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Policy # 00061

Original Effective Date: 01/28/2002

Current Effective Date: 04/20/2016

*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

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- Myeloproliferative neoplasms (MPNs), unclassifiable.

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 (MA) 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**.\*



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## **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.

## **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 “naive” 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 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 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 MA 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 MA to minimally MA 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



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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 non-MA, as opposed to fully MA (conventional) regimens.

### **Myelodysplastic Syndromes**

#### **Overview**

MDS 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% to 60% of patients, frequently involving deletions of chromosome 5 or 7, or an extra chromosome as in trisomy 8. Most MDS diagnoses occur in individuals older than age 55 to 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.

#### **Myelodysplastic Syndrome Classification and Prognosis**

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) RAEB in transformation; and, (5) CML. 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%.

The most commonly used prognostic scoring system for MDS is the International Prognostic Scoring System (IPSS), which groups patients into 1 of 4 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.

#### **Myelodysplastic Syndrome Treatment**

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 (eg, erythropoietin, darbepoetin, granulocyte colony-stimulating factor), transcriptional-modifying therapy (eg, U.S. Food and Drug Administration [FDA]-approved hypomethylating agents, nonapproved histone deacetylase inhibitors), immunomodulators (eg, lenalidomide, thalidomide, antithymocyte globulin (ATG), cyclosporine A [CYA]), low-dose chemotherapy (eg, cytarabine), and allogeneic HSCT. Given the spectrum of treatments available, the goal of therapy must



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be decided upfront, whether it is to improve anemia; thrombocytopenia; or neutropenia, eliminate the need for RBC transfusion, achieve complete remission, 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**

#### **Overview of Chronic Myeloproliferative Neoplasms**

Chronic MPNs are clonal bone marrow stem-cell disorders; as a group, an approximate total of 8400 MPNs are diagnosed annually in the United States. Like MDS, MPNs primarily occur in older individuals, with approximately 67% reported in patients aged 60 years and older.

Myeloproliferative neoplasms 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.

#### **Myeloproliferative Neoplasms Classification**

In 2008, a new WHO classification scheme replaced the term chronic myeloproliferative disorder with the term MPN. These are a subdivision of myeloid neoplasms that includes the 4 classic disorders: CML, PCV, essential thrombocytopenia, and PMF; the WHO classification also includes CNL, CEL/hypereosinophilic syndrome, MCD, and MPNs unclassifiable.

#### **Myeloproliferative Neoplasms Treatment**

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 PCV and intermediate- and high-risk PMF.

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 (MF). Ruxolitinib has been associated with improved OS, spleen size, and symptoms of MF when compared with placebo. The COMFORT-II trial compared ruxolitinib to best available therapy in patients with intermediate- and high- risk MF, and demonstrated improvements in spleen volume and OS. In a randomized trial comparing ruxolitinib with best available therapy, including antineoplastic agents, most commonly hydroxyurea, glucocorticoids, and no therapy, for MF, Harrison et al demonstrated improvements in spleen size and quality of life, but not OS.

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



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regimens for allogeneic HSCT has extended the potential benefits of this procedure to selected individuals with these disorders.

## **Rationale/Source**

### **Myelodysplastic Syndromes**

#### **Conventional Preparative Conditioning Hematopoietic Stem-Cell Transplantation for Myelodysplastic Syndromes**

Despite the successes seen with new drugs now available to treat myelodysplastic syndromes (MDS; eg, decitabine, azacitidine, lenalidomide), allogeneic HSCT is the only treatment capable of complete and permanent eradication of the MDS clone.

A 2009 review of HSCT for MDS evaluated the evidence for allogeneic HSCT with MA conditioning for MDS. The authors included 24 studies (prospective and retrospective) published between 2000 and 2008 that included a total 1378 cases with an age range of 32 to 59 years. Most patients (n=885) received matched-related donor allogeneic HSCT, with other donor types including syngeneic, matched, unrelated donor, mismatched unrelated donor, and umbilical cord blood. Most studies included de novo and secondary MDS, CML, 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 TBI, with CYA used for GVHD prophylaxis. Length of follow-up ranged from 5 months to approximately 8 years. Grades II to 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.

A review from the American Society for Blood and Marrow Transplantation (ASBMT) in 2009 assembled and evaluated the evidence related to HSCT in the therapy of MDS, with associated treatment recommendations. The authors conclude that outcomes are improved with early HSCT for patients with an IPSS score of intermediate-2 or high-risk at diagnosis, who have a suitable donor, and meet the transplant center's eligibility criteria, and for selected patients with a low or intermediate-1 risk IPSS score at diagnosis who have a poor prognostic feature not included in the IPSS (ie, older age, refractory cytopenias, etc.).

#### **Reduced Intensity Conditioning Hematopoietic Stem-Cell Transplantation for Myelodysplastic Syndromes**

Evidence from a number of largely heterogeneous, uncontrolled studies of RIC with allogeneic HSCT shows long-term remissions (ie, 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 to 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 to IV GVHD was 9% to 63%, with relapse risk of 6% to 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 et al published a randomized Phase 3 trial to compare the toxicities of 2 different conditioning regimens (reduced Cy, fludarabine, and ATG; standard Cy-ATG). Four (of 83) patients had MDS, and the

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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 MA 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 MA 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 MA chemotherapy and allogeneic HSCT are contraindicated. Nonetheless, given the absence of curative therapies for these patients, coupled with clinical input (see next), 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 MA conditioning regimen.

The 2009 ASBMT systematic review previously described addressed the evidence to support RIC compared with MA conditioning regimens and makes the following conclusions, “There are insufficient data to make a recommendation for an optimal conditioning regimen intensity. A range of dose intensities is currently being investigated, and the optimal approach will likely depend on disease and patient characteristics, such as age and comorbidities.”

Other recent reviews concur with the ASBMT recommendations.

Smaller studies continue to report outcomes from HSCT for MDS in variety of patient populations and to evaluate the impact of specific patient, conditioning, and donor characteristics on outcomes; representative studies are summarized in Table 3.

**Table 3: Case Series of HSCT Treatment for MDS**

Study	Patient Population	Type of HSCT	Summary of Outcomes
Basquiera et al (2014)	52 pediatric patients with MDS	Allo-HSCT. 59% with related donors Stem-cell source: <ul style="list-style-type: none"> <li>• Bone marrow – 63%</li> <li>• Peripheral blood – 26%</li> <li>• Umbilical cord blood – 11%</li> </ul>	5-year DFS: 50% 5-year OS: 55%
Boehm et al (2014)	60 adults with MDS or secondary AML	Allo-HSCT. MA conditioning in 36 patients; RIC conditioning in 24	10-year OS: 46%
Damaj et al (2014)	128 adults with MDS, 40 of whom received AZA	RIC allo-HSCT	3-year OS: 53% for AZA group vs. 53% for BSC



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	before HSCT and 88 who received BSC		group (p=0.69)  3-year RFS: 37% for AZA group vs. 42% for BSC group (p=0.78)  3-year NRM: 20% for AZA group vs. 23% for BSC group (p=0.74)
Di Stasi et al (2014)	227 patients with MDS or AML	Allo-HSCT. Donor source: <ul style="list-style-type: none"> <li>Matched related donor – 38%</li> <li>Matched unrelated donor – 48%</li> <li>Haploidentical – 14%</li> </ul>	3-year PFS for patients in remission: <ul style="list-style-type: none"> <li>57% for matched-related donor</li> <li>45% for matched-unrelated donor</li> <li>41% for haploidentical (p=0.417)</li> </ul>
Onida et al (2014)	523 patients with MDS treated with HSCT. IPSS cytogenetic risk group: <ul style="list-style-type: none"> <li>Good risk: 53.5%</li> <li>Intermediate risk: 24.5%</li> <li>Poor risk: 22%</li> </ul>	Allo-HSCT. RIC conditioning in 12%	5-year OS based on IPSS cytogenetic risk group: <ul style="list-style-type: none"> <li>Good risk: 48%</li> <li>Intermediate risk: 45%</li> <li>Poor risk: 30%</li> </ul>
Oran et al (2014)	256 patients with MDS. Pretreatment: <ul style="list-style-type: none"> <li>No cytoreductive chemotherapy: 30.5%</li> <li>Chemotherapy: 15.6%</li> <li>HMA: 47.7%</li> <li>Chemo+HMA: 6.2%</li> </ul>	Allo-HSCT. RIC conditioning in 36.7%	3-year EFS based on cytoreductive therapy: <ul style="list-style-type: none"> <li>No cytoreductive chemotherapy: 44.2%</li> <li>Chemotherapy: 30.6%</li> <li>HMA: 34.2%</li> <li>Chemo+HMA: 32.8% (p=0.50)</li> </ul>
Yoshimi et al (2014)	17 children with secondary MDS/AML after childhood aplastic anemia	Allo-HSCT	5-year OS and EFS: 41%.

AML – acute myelogenous leukemia; AZA – azacitidine; BSC – best supportive care; DFS – disease-free survival; HMA – hypomethylating agents; HSCT – hematopoietic stem-cell transplantation; IPSS – International Prognostic Scoring



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System; MA – myeloablative; MDS – myelodysplastic syndrome; NRM – nonrelapse mortality; OS – overall survival; RIC – reduced-intensity conditioning; RFS – relapse-free survival

### **Myeloproliferative Neoplasms**

Data on therapy for MPN remain sparse. As outlined previously in this policy, with the exception of MA 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 MA 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 an 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 was 37%, and OS was 43%, with a 3-year NRM of 32%. In a second series, 103 patients (median age, 55 years; range, 32-68 years) with intermediate to high risk (86% of total patients) PMF or post ET and PCV MF were included on a prospective multicenter Phase 2 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% to 23%) but reached 38% (95% CI, 15% to 61%) among those with a mismatched donor versus 12% (95% CI, 5% to 19%) among cases with a matched donor (p=0.003). The cumulative relapse rate at 3 and 5 years was 22% (95% CI, 13% to 31%) and 29% (95% CI, 16% to 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% to 64%) and 67% (95% CI, 55% to 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 before 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. DFS rates were 33%, 27%, and 22%, respectively. DFS 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 MF resulted in long-term relapse-free survival in about one third of patients.

Gupta et al reported better DFS rates in a more recent analysis of 233 patients with PMF who underwent RIC HSCT from 1997 to 2010. Five-year OS was 47% (95% CI, 40% to 53%). Conditioning regimen was not significantly associated with OS.

Data from direct, prospective comparison of outcomes of MA conditioning and allogeneic HSCT versus RIC and allogeneic stem-cell support in MPN are not available. However, a recent retrospective study analyzed



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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 MA 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 months (range, 20-89), there was a trend for better progression-free survival at 3 years in RIC patients compared with MA-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;  $p=0.08$ ). NRM rates at 3 years trended higher in MA-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.

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  $46\pm 12$  and  $55\pm 8$  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 and Unpublished Clinical Trials

A search of online database ClinicalTrials.gov in October 2014 identified the following phase 3 trials of hematopoietic stem-cell transplant for MDS.

- Stem Cell Transplant for Hematological Malignancy (NCT00176930) – This is a nonrandomized efficacy study to evaluate allogeneic transplant after conditioning with Cy and TBI or Cy and busulfan for multiple types of hematologic malignancies, including MDS and myeloproliferative disease. The primary outcome is progression-free survival. Enrollment is planned for 350 patients; the estimated study completion date is December 2016.
- Myeloablative Hematopoietic Progenitor Cell Transplantation (HPCT) for Pediatric Malignancies (NCT00619879) – This is a nonrandomized, safety/efficacy study to evaluate hematopoietic progenitor-cell transplantation following MA conditioning in children with hematologic malignancies, including myelodysplastic/myeloproliferative disease (primarily juvenile myelomonocytic leukemia

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and MDS and preleukemia at any stage). Enrollment is planned for 200 patients; the estimated study completion date is January 2020.

- Randomized Allogeneic Azacitidine Study (NCT00887068) – This is a randomized, safety/efficacy study to compare post-transplant azacitidine following HSCT for AML or MDS. Enrollment is planned for 246 patients; the estimated study completion date is April 2016.
- PRO#1278: Fludarabine and Busulfan vs. Fludarabine, Busulfan and Total Body Irradiation (NCT01366612) – This is a randomized, safety/efficacy study to compare the addition of TBI with fludarabine and busulfan for preconditioning for allogeneic stem-cell transplant for patients with AML, CML, other myeloproliferative disorder, or MDS. The primary outcome is relapse rate at 1 year post-transplant. Enrollment is planned for 54 patients; the estimated study completion date is December 2014.
- Fludarabine-IV Busulfan ± Clofarabine and Allogeneic Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS) (NCT01471444) – This is a randomized, safety/efficacy study to compare fludarabine-clofarabine and busulfan with fludarabine alone with busulfan for conditioning for patients with the following disorders: AML, at any stage and cytogenetic risk-group with the only exception being that patients with AML and favorable cytogenetics who achieve complete remission with 1 course of induction chemotherapy are not eligible; MDSs with intermediate- or high-risk IPSS scores or treatment-related MDS. Patients with low-risk MDS are eligible if they fail to respond to hypomethylating agent therapy such as azacitidine or decitabine. Enrollment is planned for 250 subjects; the estimated study completion date is November 2016.

### Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

In response to requests, input was received from 2 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 an MA HSCT.

### Summary

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

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### **Policy History**

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|------------|--|
| 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   |

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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.
01/08/2015	Medical Policy Committee review
01/21/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
04/07/2016	Medical Policy Committee review
04/20/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
Next Scheduled Review Date:	04/2017

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HCPCS	S2140, S2142, S2150
ICD-10 Diagnosis	C88.8 C94.40-C94.42 C94.6 D46.0-D46.1
	D46.20-D46.22 D46.4 D46.9 D46.A-D46.Z
	D47.1 D47.9 D47.Z1 D47.Z9

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- 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.

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