Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Policy Number: 8.01.21  Last Review: 1/2019
Origination: 12/2001  Next Review: 1/2020

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for allogeneic hematopoietic cell transplantation for myelodysplastic and myeloproliferative neoplasms when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Myeloablative allogeneic HSCT may be considered medically necessary as a treatment of
- myelodysplastic syndromes (see Considerations) or
- myeloproliferative neoplasms (see Considerations).

Reduced-intensity conditioning allogeneic HSCT may be considered medically necessary as a treatment of
- myelodysplastic syndromes (see Considerations) or
- myeloproliferative neoplasms (see Considerations)
in patients who for medical reasons would be unable to tolerate a myeloablative conditioning regimen. (see Considerations).

When Policy Topic is not covered
Myeloablative allogeneic HCT or reduced-intensity conditioning allogeneic HCT for myelodysplastic syndromes and myeloproliferative neoplasms that does not meet the criteria in the Considerations section is considered investigational.

Considerations
The myeloid neoplasms are categorized according to criteria developed by the World Health Organization. They are risk-stratified according to the International Prognostic Scoring System (IPSS).
2008 WHO Classification Scheme for Myeloid Neoplasms
1. Acute myeloid leukemia
2. Myelodysplastic syndromes (MDS)
3. Myeloproliferative neoplasms (MPN)
   3.1. Chronic myelogenous leukemia
   3.2. Polycythemia vera
   3.3. Essential thrombocythemia
   3.4. Primary myelofibrosis
   3.5. Chronic neutrophilic leukemia
   3.6. Chronic eosinophilic leukemia, not otherwise categorized
   3.7. Hypereosinophilic leukemia
   3.8. Mast cell disease
   3.9. MPNs, unclassifiable
4. MDS/MPN
   4.1. Chronic myelomonocytic leukemia
   4.2. Juvenile myelomonocytic leukemia
   4.3. Atypical chronic myeloid leukemia
   4.4. MDS/MPN, unclassifiable
5. Myeloid neoplasms associated with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1
   5.1. Myeloid neoplasms associate with PDGFRA rearrangement
   5.2. Myeloid neoplasms associate with PDGFRB rearrangement
   5.3. Myeloid neoplasms associate with FGFR1 rearrangement (8p11 myeloproliferative syndrome)

2008 WHO Classification of MDS
1. Refractory anemia (RA)
2. RA with ring sideroblasts (RARS)
3. Refractory cytopenia with multilineage dysplasia (RCMD)
4. RCMD with ring sideroblasts
5. RA with excess blasts 1 and 2 (RAEB 1 and 2)
6. del 5q syndrome
7. unclassified MDS

Risk Stratification of MDS
Risk stratification for MDS is performed using the IPSS. This system was developed after pooling data from 7 previous studies that used independent, risk-based prognostic factors. The prognostic model and the scoring system were built based on blast count, degree of cytopenia, and blast percentage. Risk scores were weighted relative to their statistical power. This system is widely used to divide patients into two categories: (1) low risk and (2) high-risk groups. The low-risk group includes low risk and Int-1 IPSS groups; the goals in low-risk MDS patients are to improve quality of life and achieve transfusion independence. In the high-risk group — which includes Int-2 and high-risk IPSS groups — the goals are slowing the progression of disease to AML and improving survival. The IPSS is usually calculated on diagnosis. The role of lactate dehydrogenase, marrow fibrosis, and beta 2-microglobulin also should be considered after establishing the
IPSS. If elevated, the prognostic category becomes worse by one category change.

Table 1. International Prognostic Scoring System: Myelodysplastic Syndrome Prognostic Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
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</thead>
<tbody>
<tr>
<td>Marrow blasts (5)</td>
<td>&lt; 5</td>
<td>5-10</td>
<td>11-20</td>
<td>21-30</td>
<td></td>
</tr>
<tr>
<td>Karyotype</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytopenias</td>
<td>0/1</td>
<td>2/3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. International Prognostic Scoring System: Myelodysplastic Syndrome Clinical Outcomes

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Total score</th>
<th>Median survival, yrs</th>
<th>Time for 25% to progress to AML, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>5.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>0.5-1.0</td>
<td>3.5</td>
<td>3.3</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>1.5-2.0</td>
<td>1.2</td>
<td>1.12</td>
</tr>
<tr>
<td>High</td>
<td>2.5 or more</td>
<td>0.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

AML: acute myelocytic leukemia.

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. (1) 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.

Given the long natural history of MDS, allogeneic HSCT is typically considered in those with increasing numbers of blasts, signaling a possible transformation to acute myeloid leukemia. Subtypes falling into this category include refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, or chronic myelomonocytic leukemia.

Patients with refractory anemia with or without ringed sideroblasts may be considered candidates for allogeneic HSCT when chromosomal abnormalities are present or the disorder is associated with the development of significant cytopenias (e.g., neutrophils less 500/mm3, platelets less than 20,000/mm3).

Patients with MPNs may be considered candidates for allogeneic HSCT when there is progression to myelofibrosis, or when there is evolution toward acute leukemia. In addition, allogeneic HSCT may be considered in patients with essential thrombocythemia with an associated thrombotic or hemorrhagic disorder. There are no suitable U.S. Food and Drug Administration (FDA) -approved therapies for these patients, only supportive care. The use of allogeneic HSCT should be based on cytopenias, transfusion dependence, increasing blast percentage over 5%, and age.
Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for RIC allogeneic HSCT. These include those patients whose age (typically older than 60 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen. The ideal allogeneic donors are HLA-identical siblings, matched at the HLA-A, B, and DR loci (6 of 6). Related donors mismatched at one locus are also considered suitable donors. A matched, unrelated donor (MUD) identified through the National Marrow Donor Registry is typically the next option considered. Recently, there has been interest in haploidentical donors, typically a parent or a child of the patient, where usually there is sharing of only 3 of the 6 major histocompatibility antigens. The majority of patients will have such a donor; however, the risk of GVHD and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

Clinical input suggests RIC allogeneic HSCT may be considered for patients as follows:

**MDS**
- IPSS intermediate-2 or high risk
- RBC transfusion dependence
- Neutropenia
- Thrombocytopenia
- High risk cytogenetics
- Increasing blast percentage

**MPN**
- Cytopenias
- Transfusion dependence
- Increasing blast percentage over 5%
- Age 60-65 years

### Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Individuals: With myelodysplastic syndromes</td>
<td>Interventions of interest are: • Myeloablative conditioning allogeneic hematopoietic cell transplant</td>
<td>Comparators of interest are: • Standard of care</td>
<td>Relevant outcomes include: • Overall survival • Disease-specific survival • Treatment-related mortality • Treatment-related morbidity</td>
</tr>
<tr>
<td>Individuals: With myelodysplastic syndromes</td>
<td>Interventions of interest are: • Reduced-intensity conditioning allogeneic hematopoietic cell transplant</td>
<td>Comparators of interest are: • Standard of care</td>
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<td>Interventions of</td>
<td>Comparators of</td>
<td>Relevant outcomes include:</td>
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</table>
Myelodysplastic syndromes and myeloproliferative neoplasms refer to a heterogeneous group of clonal hematopoietic disorders with the potential to transform into acute myelocytic leukemia (AML). Allogeneic hematopoietic cell transplantation (HCT) has been proposed as a curative treatment option for patients with these disorders.

For individuals who have MDS or 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 have reported a relatively large range of overall and progression-free survival rates, which reflect the heterogeneity in patient populations, conditioning regimens, and other factors. Reported estimates for 3- to 5-year overall survival of 40% to 50% are typical. For HCT for MPN, data are more limited. At least 1 comparative study of HCT for myelofibrosis has 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 or MPN who receive reduced-intensity conditioning (RIC) 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 has suggested that RIC may be used in patients who are older and have 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. HCT is at present the only potentially curative treatment option for patients with MDSs and MPN. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Background**

**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.

**MDS Classification and Prognosis**

The French-American-British (FAB) system was used to classify MDS into 5 subtypes as follows: (1) refractory anemia; (2) refractory anemia with ringed sideroblasts; (3) refractory anemia with excess blasts; (4) refractory anemia with excess blasts in transformation; and (5) chronic myelomonocytic leukemia. The FAB system was 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 (eg, peripheral blood counts, 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 WHO classification-based Prognostic Scoring System 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.

**MDS 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, cyclosporine A), low-dose chemotherapy (eg, 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 red blood cell transfusion, achieve complete remission, or cure the disease.

Allogeneic HCT 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 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.

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.

**MPN Classification**

In 2008, a new WHO classification scheme replaced the term chronic myeloproliferative disorder with the term myeloproliferative neoplasms (MPN). These are a subdivision of myeloid neoplasms that includes the 4 classic disorders: chronic myeloid leukemia (CML), polycythemia vera, essential thrombocytopenia, and primary myelofibrosis; the WHO classification also includes chronic neutrophilic leukemia, chronic eosinophilic leukemia/hypereosinophilic syndrome, mast cell disease, and MPNs unclassifiable.

**MPN 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 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.(2) The COMFORT-II trial compared ruxolitinib to best available therapy in patients with intermediate- and high-risk myelofibrosis, and demonstrated improvements in spleen volume and OS.(3) In a randomized trial comparing ruxolitinib with 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.(4)

MA allogeneic 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, the use of RIC of conditioning regimens for allogeneic HCT has extended the potential benefits of this procedure to selected individuals with these disorders.

**Hematopoietic Cell Transplantation**

Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allo-HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naive” and thus are associated with a lower incidence of rejection or graft-versus-host disease. Cord blood is discussed in greater detail in separate policy.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is critical for achieving a good outcome of allo-HCT. Compatibility is established by typing of human leukocyte antigen (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 HCT**

The conventional (“classical”) practice of allo-HCT involves administration of cytotoxic agents (eg, cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect of this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy effect that develops after engraftment of allogeneic stem cells within the patient’s bone marrow space. While the slower graft-versus-malignancy 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 events that include preengraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allo-HCT, immune suppressant drugs are required to minimize graft rejection and graft-versus-host disease, which also increases susceptibility of the patient to opportunistic infections.
Reduced-Intensity Conditioning for Allo-HCT
Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden and to minimize as much as possible associated treatment-related morbidity and nonrelapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of nonrelapse mortality and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative to minimally myeloablative with lymphoablation, and intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For this evidence review, RIC will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

Regulatory Status
The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

Rationale
This evidence review was created in December 1999 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through November 15, 2017.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled
trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice. The following is a summary of the key literature to date.

**Myelodysplastic Syndromes**

**Myeloablative Conditioning Allogeneic Hematopoietic Cell Transplantation**

Despite the successes seen with drugs now available to treat myelodysplastic syndromes (MDS; eg, decitabine, azacitidine, lenalidomide), allogeneic hematopoietic cell transplantation (allo-HCT) is the only treatment capable of complete and permanent eradication of the MDS clone. A 2009 review of HCT for MDS evaluated the evidence for allo-HCT with myeloablative conditioning (MAC) for MDS. Reviewers selected 24 studies (prospective and retrospective) published between 2000 and 2008 that included a total 1378 cases (age range, 32-59 years). Most patients (n=885) received matched-related donor allo-HCT, with other donor types including syngeneic, matched, unrelated donor, mismatched unrelated donor, and umbilical cord blood. Most studies included de novo and secondary MDS, chronic myelomonocytic leukemia, myeloproliferative neoplasms (MPN), de novo and secondary acute myeloid leukemia (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 (CY) and CY plus total body irradiation, with cyclosporine A (CYA) used for graft-versus-host disease (GVHD) prophylaxis. Length of follow-up ranged from 5 months to approximately 8 years. Acute GVHD (grades II-IV) varied from 18% to 100%. Relapse risk ranged from 24% at 1 year to 36% at 5 years. Overall survival (OS) rates ranged from 25% at 2 years to 52% at 4 years, with nonrelapse mortality (NRM) ranging from 19% at day 100 to 61% at 5 years.

A 2009 review from the American Society for Blood and Marrow Transplantation (ASBMT) evaluated the evidence related to HCT in the therapy of MDS, with associated treatment recommendations. Reviewers concluded that outcomes improved with early HCT for patients with an International Prognostic Scoring System (IPSS) score of intermediate-2 or high-risk at diagnosis who had a suitable donor and met the transplant center’s eligibility criteria, and for selected patients with a low or intermediate-1 risk IPSS score at diagnosis who had a poor prognostic feature not included in the IPSS (ie, older age, refractory cytopenias). Koenecke et al (2015) evaluated the impact on the revised 5-category IPSS score (IPSS-5) on outcomes after HCT in patients with MDS or secondary AML (evolved from MDS). In a cohort of 903 patients retrospectively identified from the European Society for Blood and Marrow Transplantation database, those with poor and very poor risk had shorter relapse-free survival (RFS) and OS than those with very good, good, or intermediate risk. However, the ways that transplant
management strategies should change based on cytogenetic abnormalities are not currently well defined.

**Reduced-Intensity Conditioning Allo-HCT for MDS**

Evidence from a number of largely heterogeneous, uncontrolled studies of reduced-intensity conditioning (RIC) with allo-HCT has shown long-term remission (ie, >4 years) can be achieved, often with reduced treatment-related morbidity and mortality, in patients with MDS or AML who otherwise would not be candidates for MAC regimens.\(^6\)\(^9\)\(^1\)\(^9\)\(^1\)\(^9\)\(^1\)\(^9\) These prospective and retrospective studies included cohorts of 16 to 215 patients similar to those in the MAC allo-HCT 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%. OS rates ranged between 44% at 1 year and 46% at 5 years (median follow-up range, 14 months to >4 years).

Zeng et al (2014) conducted a systematic review and meta-analysis comparing outcomes for patients who had MDS or AML treated with HCT plus RIC or MAC.\(^2\)\(^0\) Reviewers included 8 studies (2 prospective, 8 retrospective), with a total of 6464 AML or MDS patients. Of these, 171 received RIC and 4893 received MAC. Overall, RIC-treated patients were older and more likely to have multiple comorbidities. In pooled analysis, OS, RFS, and NRM did not differ significantly between patients receiving RIC and MAC. Relapse incidence was significantly lower in the MAC arm (odds ratio for RIC vs MAC, 1.41; 95% confidence interval [CI], 1.24 to 1.59; \(p<0.001\)).

Aoki et al (2015) compared RIC with MAC in a retrospective cohort of 448 patients (age range, 50-69 years) with advanced MDS (refractory anemia with excess blasts or refractory anemia in transformation).\(^2\)\(^1\) Of the total, 197 (44%) and 251 (56%) received MAC or RIC, respectively. The groups differed at baseline: patients who received RIC were significantly more likely to be 60 to 69 years old (vs 50-59 years; 47% for RIC vs 47% for MAC; \(p=0.001\)), and less likely to receive an unrelated donor transplant (54% vs 70%; \(p=0.001\)). Three-year OS rates did not differ between groups (44.1% for RIC vs 42.7% for MAC; \(p=0.330\)). Although patients treated with RIC had a significantly lower 3-year cumulative incidence of NRM (25.6% vs 37.9%; \(p=0.002\)), they had significantly higher 3-year incidence of relapse than patients treated with MAC (29.9% vs 22.8%; \(p=0.029\)).

In 2012, Kim et al published a phase 3 randomized trial (N=83 patients) comparing toxicity rates for 2 conditioning regimens (reduced CY, fludarabine, and antithymocyte globulin [ATG]; standard CY-ATG).\(^2\)\(^2\) Four patients had MDS, and the remaining patients had severe aplastic anemia. Overall, the incidence of reported toxicities was lower in patients receiving the RIC 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 a higher relapse rate than with MAC allo-HCT. However, in the absence of
prospective, comparative, randomized trials, only indirect comparisons can be made between the relative clinical benefits and harms associated with MAC and RIC regimens with allo-HCT. Furthermore, no published randomized trials have compared RIC plus allo-HCT with conventional chemotherapy alone, which has been the standard of care in patients with MDS and AML for whom MAC chemotherapy and allo-HCT are contraindicated.

The American Society for Blood and Marrow Transplantation’s 2009 systematic review (previously described) assessed the evidence supporting RIC and MAC regimens and drew 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 reviews (2010-2012) have also drawn conclusions similar to those of the American Society for Blood and Marrow Transplantation. Given the absence of curative therapies for these patients, however, RIC allo-HCT may be considered a treatment for patients with MDS who could benefit from allo-HCT but who for medical reasons would not tolerate a MAC regimen.

**Outcomes After Allo-HCT in Mixed MDS Populations**

A number of studies, primarily retrospective, continue to report outcomes from allo-HCT for MDS in a variety of patient populations and to evaluate the impact of specific patient, conditioning, and donor characteristics on outcomes; representative studies are summarized in Table 1.

**Table 1. Case Series of HCT Treatment for MDS**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>Type of HCT</th>
<th>Summary of Outcomes</th>
</tr>
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<tbody>
<tr>
<td><strong>Basquiera et al (2015)</strong></td>
<td>52 pediatric patients with MDS</td>
<td>Allo-HCT (59% with related donors)</td>
<td>5-y DFS=50%</td>
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<tr>
<td></td>
<td></td>
<td>Stem cell source:</td>
<td>5-y OS=55%</td>
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<tr>
<td></td>
<td></td>
<td>o Bone marrow, 63%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>o Peripheral blood, 26%</td>
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<tr>
<td></td>
<td></td>
<td>o Umbilical cord blood, 11%</td>
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<tr>
<td><strong>Boehm et al (2014)</strong></td>
<td>60 adults with MDS or secondary AML</td>
<td>Allo-HCT</td>
<td>10-y OS=46%</td>
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<tr>
<td></td>
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<td>MAC in 36 patients; RIC in 24 patients</td>
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<tr>
<td><strong>Damaj et al (2014)</strong></td>
<td>128 adults with MDS: 40 received AZA before HCT and 88 received BSC</td>
<td>RIC allo-HCT</td>
<td>3-y OS=53% in AZA group vs 53% in BSC group (p=0.69)</td>
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<td></td>
<td>3-y RFS=37% in AZA group vs 42% in BSC group (p=0.78)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3-y NRM=20% in AZA group vs 23% in BSC group (p=0.74)</td>
</tr>
<tr>
<td><strong>Di Stasi et</strong></td>
<td>227 patients with MDS or</td>
<td>Allo-HCT</td>
<td>3-y PFS for patients in</td>
</tr>
<tr>
<td>Study</td>
<td>Patient Population</td>
<td>Type of HCT</td>
<td>Summary of Outcomes</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------------------</td>
<td>---------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>al (2014)</td>
<td>AML</td>
<td></td>
<td>• Donor source:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>o Matched-related, 38%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>o Matched-unrelated, 48%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>o Haploidentical, 14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>remission:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 57% for matched-related</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 45% for matched-unrelated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 41% for haploidentical (p=0.417)</td>
</tr>
<tr>
<td>Onida et al (2014)</td>
<td>523 patients with MDS</td>
<td>Allo-HCT</td>
<td>5-y OS based on IPSS cytogenic risk group:</td>
</tr>
<tr>
<td></td>
<td>IPSS cytogenic risk group:</td>
<td>RIC in 12%</td>
<td>• Good: 48%</td>
</tr>
<tr>
<td></td>
<td>o Good risk: 53.5%</td>
<td></td>
<td>• Intermediate: 45%</td>
</tr>
<tr>
<td></td>
<td>o Intermediate risk: 24.5%</td>
<td></td>
<td>• Poor: 30%</td>
</tr>
<tr>
<td></td>
<td>o Poor risk: 22%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oran et al (2014)</td>
<td>256 patients with MDS</td>
<td>Allo-HCT</td>
<td>3-y EFS based on cytoreductive therapy:</td>
</tr>
<tr>
<td></td>
<td>Pretreatment:</td>
<td>RIC in 36.7%</td>
<td>• No cytoreductive chemo: 44.2%</td>
</tr>
<tr>
<td></td>
<td>o No cytoreductive chemo: 30.5%</td>
<td></td>
<td>• Chemo: 30.6%</td>
</tr>
<tr>
<td></td>
<td>o Chemo: 15.6%</td>
<td></td>
<td>• HMA: 34.2%</td>
</tr>
<tr>
<td></td>
<td>o HMA: 47.7%</td>
<td></td>
<td>• Chemo + HMA: 32.8% (p=0.50)</td>
</tr>
<tr>
<td>Yoshimi et al (2014)</td>
<td>17 children with secondary MDS or AML or AML after childhood aplastic anemia</td>
<td>Allo-HCT</td>
<td>5-y OS and EFS=41%</td>
</tr>
<tr>
<td>Basquiera et al (2016)</td>
<td>84 adults with MDS</td>
<td>Allo-HCT</td>
<td>OS:</td>
</tr>
<tr>
<td></td>
<td>Cytogenic risk group:</td>
<td>RIC in 31.1%</td>
<td>• Median: 23.5 mo (95% CI, 1.7 to 45.3 mo)</td>
</tr>
<tr>
<td></td>
<td>o Standard: 65.5%</td>
<td></td>
<td>• 1-y=61% (95% CI, 50% to 70%)</td>
</tr>
<tr>
<td></td>
<td>o Adverse: 12.6%</td>
<td></td>
<td>• 4-y=38% (95% CI, 27% to 49%)</td>
</tr>
<tr>
<td></td>
<td>o Unknown: 21.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symeonidis et al (2015)</td>
<td>513 adults with CMML</td>
<td>Allo-HCT</td>
<td>PFS:</td>
</tr>
<tr>
<td></td>
<td>Pretreatment:</td>
<td>RIC in 41.6%</td>
<td>• Median: 19.9 mo (95% CI, 9 to 31 mo)</td>
</tr>
<tr>
<td></td>
<td>o No prior disease-modifying therapy: 28%</td>
<td></td>
<td>• 1-y=57% (95% CI, 46% to 67%)</td>
</tr>
<tr>
<td></td>
<td>o Disease-modifying therapy: 72%</td>
<td></td>
<td>• 4-y=37% (95% CI, 26% to 48%)</td>
</tr>
<tr>
<td>Pohlen et al (2016)</td>
<td>187 patients with refractory AML (87%) or high-risk MDS (13%)</td>
<td>Allo-HCT</td>
<td>3-y RFS=32% (95% CI, 25% to 39%)</td>
</tr>
<tr>
<td></td>
<td>Stem cell source:</td>
<td>RIC in 52%</td>
<td>3-y OS=35% (95% CI, 27% to 42%)</td>
</tr>
<tr>
<td></td>
<td>o Bone marrow, 6%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Study  |  Patient Population  |  Type of HCT  |  Summary of Outcomes  
---  |  ---  |  ---  |  ---  
Heidenreich et al (2017)³⁰  |  313 adults with MDS and secondary AML, age ≥ 70 Cytogenic risk group:  
- Good: 51%  
- Intermediate: 22%  
- Poor/very poor: 11%  |  Allo-HCT  
- RIC or non-MAC in 83%  
- Unrelated donors in 75%  
- Stem cell source:  
  - Bone marrow, 6%  
  - Peripheral blood, 94%  |  1-y NRM: 32%  
3-y relapse: 28%  
3-y OS: 34%

---

**Section Summary: Myelodysplastic Syndromes**

Primarily uncontrolled, observational studies of HCT for MDS have reported a relatively large range of OS and progression-free survival values, which reflect the heterogeneity in patient populations, conditioning regimens, and other factors. Reported estimates for 3- to 5-year OS of 40% to 50% are typical. Direct comparisons between RIC and MAC prior to HCT with randomly selected populations are not available. Evidence from nonrandomized comparisons has suggested that RIC may be used in patients who are older and with more comorbidities without significantly worsening OS. RIC appears to be associated with lower rates of NRM but higher cancer relapse than MAC HCT.

**Myeloproliferative Neoplasms**

Data on therapy for myeloproliferative neoplasms (MPN) are sparse.¹⁶,⁴⁰,⁴¹ As outlined in this evidence review, with the exception of MAC chemotherapy and allo-HCT, no therapy has yet proven to be curative or to prolong survival of patients with MPN.

The largest study identified evaluating allo-HCT for primary myelofibrosis comes from a 2010 analysis of the outcomes for 289 patients treated between 1989 and 2002, from the database of the Center for International Bone Marrow Transplant Research.⁴² Median age was 47 years (range, 18–73 years). Donors were human leukocyte antigen (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. Disease-free survival (DFS) rates were 33%, 27%, and 22%, respectively. DFS for patients receiving RIC allo-HCT was comparable: 39% for HLA-identical sibling donors and 17% for unrelated donors at 3 years. In this large retrospective series, allogeneic

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**Abbreviations:** allo; allogeneic; AML: acute myelogenous leukemia; AZA: azacitidine; BSC: best supportive care; chemo: chemotherapy; CI: confidence interval; CMML: chronic myelomonocytic leukemia; DFS: disease-free survival; HMA: hypomethylating agents; HCT: hematopoietic cell transplantation; IPSS: International Prognostic Scoring System; MAC: myeloablative conditioning; MDS: myelodysplastic syndromes; NRM: nonrelapse mortality; OS: overall survival; RFS: relapse-free survival; RIC: reduced-intensity conditioning.
transplantation for myelofibrosis resulted in long-term RFS in about one-third of patients.

Gupta et al reported better DFS rates in a 2014 analysis of 233 patients with primary myelofibrosis who underwent RIC HCT from 1997 to 2010. The 5-year OS rate was 47% (95% CI, 40% to 53%). Conditioning regimen was not significantly associated with OS.

In another relatively large study that included patients with primary myelofibrosis who were under 65 years old at diagnosis, Kroger et al (2015) compared outcomes for patients treated with allo-HCT (n=190) or conventional therapies (n=248) at diagnosis. In the HCT group, 91 and 97 subjects received RIC and MAC, respectively. Patients at low risk based on the Dynamic International Prognostic Scoring System model treated with HCT had a relative risk of death, compared with conventionally treated patients, of 5.6 (95% CI, 1.7 to 19; p=0.005). In contrast, those with intermediate-2 and high-risk disease treated with HCT had a relative risk of death, compared with conventionally treated patients, of 0.55 (95% CI, 0.36 to 0.83; p=0.005) and 0.37 (95% CI, 0.21 to 0.66; p<0.001), respectively. Intermediate-1 patients treated with HCT did not differ significantly in risk of death from those treated with conventional therapies. Although the study design was limited by the potential for bias due to patient selection, these results support using prognosis to guide decisions about HCT for primary myelofibrosis.

The significant toxicity of MAC plus allo-HCT in MPN has led to study of RIC regimens for these diseases. Data from direct, prospective comparison of outcomes of MAC and allo-HCT vs RIC and allogeneic stem cell support in MPN are not available, but single-arm series and nonrandomized comparative studies have reported outcomes after RIC allo-HCT. One 2008 series included 27 patients (mean age, 59 years) with MPN who underwent allo-HCT using an RIC regimen of low-dose (2 gray) total body irradiation alone with or without fludarabine. At a median follow-up of 47 months, 3-year RFS was 37%, 3-year OS was 43%, and 3-year NRM was 32%. In a second series (2009), 103 patients (median age, 55 years; range, 32-68 years) with intermediate-to-high risk (86% of total patients) primary myelofibrosis or postessential thrombocythemia and polycythemia vera were included in a prospective, multicenter, phase 2 trial to determine the efficacy of a busulfan plus fludarabine-based RIC regimen followed by allo-HCT from related (n=33) or unrelated (n=70) donors. Acute GVHD (grade II-IV) occurred in 27% of patients, and chronic GVHD in 43%. The cumulative incidence of NRM at 1 year in all patients was 16% (95% CI, 9% to 23%), but reached 38% (95% CI, 15% to 61%) among those with a mismatched donor vs 12% (95% CI, 5% to 19%) among cases with a matched donor (p=0.003). The cumulative relapse rates at 3 and 5 years were 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), the 5-year estimated DFS and OS rates were 51% (95% CI, 38% to 64%) and 67% (95% CI, 55% to 79%), respectively.
A 2009 retrospective study analyzed the impact of conditioning intensity on outcomes for allo-HCT in patients with myelofibrosis. 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 MAC 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 months), there was a trend for a better progression-free survival rate at 3 years in RIC patients than in MAC patients (58% [range, 23%-62%] vs 43% [range, 35%-76%], respectively; p=0.11); there was a similar trend in the 3-year OS rate (68% [range, 45%-84%] vs 48% [range, 27%-66%], respectively; p=0.08). NRM rates at 3 years trended higher in MAC cases (48%; range, 31%-74%) than in RIC cases (27%; range, 14%-55%; p=0.08). The results of this study suggested that both types of conditioning regimens have curative potential in patients with myelofibrosis. 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 allo-HCT in this population.

In a 2012 retrospective study in 9 Nordic transplant centers, 92 patients with myelofibrosis in chronic phase underwent allo-HCT. MAC was given to 40 patients and RIC to 52 patients. Mean age in the 2 groups at transplantation was 46 and 55 years, respectively (p<0.001). When adjustment for age differences was made, 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 survival. No significant difference was found in NRM at 100 days between the MAC- and the RIC-treated patients. The probability of survival at 5 years was 49% for the MAC group and 59% in the RIC group (p=0.125). Patients treated with RIC experienced significantly less acute GVHD than in patients treated with MAC (p<0.001). The OS rates at 5 years were 70%, 59% and 41% for patients with Lille scores 0, 1, and 2, respectively (p=0.038, when adjusting for age). Furthermore, 21% of patients in the RIC group were given donor lymphocyte infusion because of incomplete donor chimerism, compared with none of the MAC-treated patients (p<0.002); 9% of patients needed a second transplant because of graft failure, disease progression, or transformation to AML, with no significant differences between groups.

**Section Summary: Myeloproliferative Neoplasms**

Observational studies of HCT for MPN have reported a range of 3- to 5-year OS rates from 35% to 50% and suggested that HCT may be associated with improved survival in patients with intermediate-2 and high-risk disease. Currently, only retrospective studies have compared the RIC and MAC regimens. While these nonrandomized comparisons have suggested that RIC may be used in patients who are older and who have poorer performance status without significantly worsening OS, randomized trials are needed to provide greater certainty in the efficacy of the conditioning regimens.
Summary of Evidence
For individuals who have MDS or 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 mortality and morbidity. Primarily uncontrolled, observational studies of HCT for MDS have reported a relatively large range of overall and progression-free survival rates, which reflect the heterogeneity in patient populations, conditioning regimens, and other factors. Reported estimates for 3- to 5-year overall survival of 40% to 50% are typical. For HCT for MPN, data are more limited. At least 1 comparative study of HCT for myelofibrosis has demonstrated improved survival using HCT compared with standard therapy. At present, HCT is 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 or MPN who receive RIC allo-HCT, the evidence includes primarily retrospective observational series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. 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 has suggested that RIC may be used in patients who are older and have 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. At present, HCT is 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.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers
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.

In response to requests, input was received from 2 academic medical center specialists while this policy was under review in 2009. There was a consensus among reviewers that reduced-intensity conditioning allogeneic hematopoietic cell transplantation was of value in patients with myelodysplastic syndromes and myeloproliferative neoplasms who would be medically unable to tolerate a myeloablative hematopoietic cell transplantation.
Practice Guidelines and Position Statements

Current National Comprehensive Cancer Network (NCCN) clinical guidelines for myelodysplastic syndromes (MDS; v.1.2018) make the following general recommendation about allogeneic hematopoietic cell transplantation (allo-HCT):

“For patients who are transplant candidates, the first choice of a donor has remained an HLA [human leukocyte antigen]-matched sibling, although results with HLA-matched unrelated donors have improved to levels comparable to those obtained with HLA-matched siblings. With the increasing use of cord blood or HLA-haploidentical related donors, HCT has become a viable option for many patients. High-dose conditioning is typically used for younger patients, whereas RIC [reduced-intensity conditioning] for HCT is generally the strategy in older individuals.”

Specific NCCN recommendations for HCT for treatment of MDS are outlined in Table 2.

Table 2. Guidelines for Allo-HCT for Myelodysplastic Syndromes

<table>
<thead>
<tr>
<th>Prognostic Category</th>
<th>Recommendations for Allo-HCT</th>
</tr>
</thead>
</table>
| IPSS low/intermediate-1 OR IPSS-R very low, low, intermediate OR WPSS very low, low, intermediate | • Consider allo-HCT for patients who have clinically relevant thrombocytopenia or neutropenia or increased marrow blasts, with disease progression or no response after azacitidine/decitabine or immunosuppressive therapy  
• Consider allo-HCT for patients who have symptomatic anemia with no 5q deletion, with serum erythropoietin level >500 mU/mL, with poor probability of response to immunosuppressive therapy, and no response or intolerance to azacitidine/decitabine or immunosuppressive therapy |
| IPSS intermediate-2, high OR IPSS-R intermediate, high, very high OR WPSS high, very high | • Recommend allo-HCT if a high-intensity therapy candidate and transplant candidate and donor stem cell source is available |


Table 3 summarizes the NCCN recommendations (v.2.2018) on the use of allo-HCT for the treatment of myeloproliferative neoplasms (MPN). The guidelines note that selection of allo-HCT should be based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver.

Table 3. Guidelines for Allo-HCT for Myeloproliferative Neoplasms

<table>
<thead>
<tr>
<th>Prognostic Category</th>
<th>Recommendations for Allo-HCT</th>
</tr>
</thead>
</table>
| Intermediate risk – 1 myelofibrosis IPSS=1 DIPSS-Plus=1 DIPSS=1 or 2 | • Consider observation or ruxolitinib if symptomatic or allo-HCT.  
• Evaluation for allo-HCT is recommended for patients with low platelet counts or complex cytogenetics |
| Intermediate risk – 2 myelofibrosis | • Consider allo-HCT immediately or bridging |
IPSS=2  
DIPSS-Plus=2 or 3  
DIPSS=3 or 4  
High-risk myelofibrosis  
IPSS>3  
DIPSS-Plus=4 to 6  
DIPSS=5 or 6

therapy can be used to decrease marrow blasts to an acceptable level prior to transplant.  
• Evaluation for allo-HCT is recommended for patients with low platelet counts or complex cytogenetics

Disease progression to advanced stage/AML

• Induce remission with hypomethylating agents or intensive induction chemotherapy followed by allo-HCT


American Society for Blood and Marrow Transplantation
In 2015, the American Society for Blood and Marrow Transplantation published guidelines on indications for HCT, based on the recommendations of a multiple-stakeholder task force. Table 4 summarizes categorizations for allo-HCT.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myelodysplastic syndromes</strong></td>
<td></td>
</tr>
<tr>
<td>Low/intermediate-1 risk</td>
<td>Standard of care, clinical evidence available (large clinical trials are not available; however, sufficiently large cohort studies have shown efficacy with “acceptable risk of morbidity and mortality”)</td>
</tr>
<tr>
<td>Intermediate-2/high risk</td>
<td>Standard of care (“well defined and generally supported by evidence in the form of high quality clinical trials and/or observational studies”)</td>
</tr>
<tr>
<td><strong>Myelofibrosis and myeloproliferative neoplasms</strong></td>
<td></td>
</tr>
<tr>
<td>Primary, low risk</td>
<td>Standard of care (“well defined and generally supported by evidence in the form of high quality clinical trials and/or observational studies”)</td>
</tr>
<tr>
<td>Primary, intermediate/high risk</td>
<td>Standard of care (“well defined and generally supported by evidence in the form of high quality clinical trials and/or observational studies”)</td>
</tr>
<tr>
<td>Secondary</td>
<td>Standard of care (“well defined and generally supported by evidence in the form of high quality clinical trials and/or observational studies”)</td>
</tr>
<tr>
<td>Hypereosinophilic syndromes, refractory</td>
<td>Standard of care, rare indication (clinical trials and observational studies are not feasible due to low incidence; small cohorts have shown efficacy with “acceptable risk of morbidity and mortality”)</td>
</tr>
</tbody>
</table>

European Blood and Marrow Transplantation Group and European LeukemiaNet
In 2015, the European Blood and Marrow Transplantation and European LeukemiaNet Group published recommendations for the use of allo-HCT in primary myelofibrosis and for pre- and posttransplant management and donor selection. Recommendations related to the selection of patients for allo-HCT included:

- “All patients with intermediate-2 or high-risk disease according to IPSS, DIPSS [Dynamic International Prognostic Scoring System], or DIPSS+, and age < 70
years, should be considered potential candidates for allo-SCT [stem cell transplant].”

▪ “Patients with intermediate-1-risk disease and age <65 years should be considered candidates for allo-SCT [stem cell transplant] if they present with either refractory, transfusion-dependent anemia or a percentage of blasts in PB [peripheral blood] >2%, or adverse cytogenetics (as defined by the DIPSS+ classification).”

▪ “Patients with low-risk disease should not undergo allo-SCT. They should be monitored and evaluated for transplantation when disease progression occurs.”

▪ “Patients in blast transformation (blasts in PB or in BM [bone marrow] or both equal to or >20%) are not good candidates for allo-SCT. They should receive debulking therapy and be reconsidered for transplant after achieving a partial or complete remission of leukemia.”

▪ “Although the use of molecular risk classification for the identification of candidates for allo-SCT among intermediate-1- risk patients deserves further clinical validation, patients in this risk category who are triple negative (that is, JAKV617F, CALR, and MPL negative) or ASXL1 positive, or both, should be considered for allo-SCT.”

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is a national coverage determination for stem cell transplantation (110.23; formerly 110.81),52 portions of which are highlighted below:

“B. Nationally Covered Indications

I. Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)
   a) …Treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary,
   b) …Treatment of severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome.
   c) …Treatment of Myelodysplastic Syndromes (MDS) pursuant to Coverage with Evidence Development (CED) in the context of a Medicare-approved, prospective clinical study.

   Medicare payment for these beneficiaries will be restricted to patients enrolled in an approved clinical study.

d) Effective … January 27, 2016, allogeneic HSCT for multiple myeloma is covered by Medicare only for beneficiaries with Durie-Salmon Stage II or III multiple myeloma, or International Staging System (ISS) Stage II or Stage III multiple myeloma, and participating in an approved prospective clinical study that meets the criteria below. There must be appropriate statistical techniques to control for selection bias and confounding by age, duration of diagnosis, disease classification, International Myeloma Working Group (IMWG) classification, ISS stage, comorbid conditions, type of
preparative/conditioning regimen, graft vs. host disease (GVHD) prophylaxis, donor type and cell source.

e) Effective ... January 27, 2016, allogeneic HSCT for myelofibrosis (MF) is covered by Medicare only for beneficiaries with Dynamic International Prognostic Scoring System (DIPSSplus) intermediate-2 or High primary or secondary MF and participating in an approved prospective clinical study. All Medicare approved studies must use appropriate statistical techniques in the analysis to control for selection bias and potential confounding by age, duration of diagnosis, disease classification, DIPSSplus score, comorbid conditions, type of preparative/conditioning regimen, graft vs. host disease (GVHD) prophylaxis, donor type and cell source.

f) Effective ... January 27, 2016, allogeneic HSCT for sickle cell disease (SCD) is covered by Medicare only for beneficiaries with severe, symptomatic SCD who participate in an approved prospective clinical study.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 5.

Table 5. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00176930</td>
<td>Allogeneic Transplant for Hematological Malignancy</td>
<td>350</td>
<td>Dec 2017</td>
</tr>
<tr>
<td>NCT02581007</td>
<td>Reduced Intensity Conditioning and Transplantation of Partially HLA-Mismatched Peripheral Blood Stem Cells for Patients with Hematologic Malignancies</td>
<td>30</td>
<td>Feb 2018</td>
</tr>
<tr>
<td>NCT00887068</td>
<td>Randomized Controlled Study of Post-transplant Azacitidine for Prevention of Acute Myelogenous Leukemia and Myelodysplastic Syndrome Relapse</td>
<td>246</td>
<td>Apr 2018</td>
</tr>
<tr>
<td>NCT00739141</td>
<td>Conditioning Regimen and the Transplantation of Unrelated Donor Umbilical Cord Blood in Patients with Hematologic Malignancies</td>
<td>80</td>
<td>Aug 2018</td>
</tr>
<tr>
<td>NCT01366612</td>
<td>PRO#1278: A Phase III Study of Fludarabine and Busulfan Versus Fludarabine, Busulfan and Low Dose Total Body Irradiation in Patients Receiving an Allogeneic Hematopoietic Stem Cell Transplant</td>
<td>54</td>
<td>Aug 2018</td>
</tr>
<tr>
<td>NCT01471444a</td>
<td>A Randomized Study of Once Daily Fludarabine-Clofarabine Versus Fludarabine Alone Combined With Intravenous Busulfan Followed by Allogeneic Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS)</td>
<td>250</td>
<td>Nov 2018</td>
</tr>
<tr>
<td>NCT00822393</td>
<td>Clinical Phase III Trial Treosulfan-Based Conditioning Versus Reduced-Intensity Conditioning (RIC) Prior to Allogeneic Hematopoietic Stem Cell Transplantation in</td>
<td>960</td>
<td>Mar 2019</td>
</tr>
<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
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<td>---------------</td>
<td>----------------------------------------------------------------------------</td>
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<tr>
<td>NCT02626715</td>
<td>Reduced Intensity Conditioning (RIC) and Myeloablative Conditioning (MAC) for HSCT in AML/MDS</td>
<td>16</td>
<td>Sep 2019</td>
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<tr>
<td>NCT01760655</td>
<td>Reduced Intensity Conditioning Before Donor Stem Cell Transplant in Treating Patients with High-Risk Hematologic Malignancies</td>
<td>50</td>
<td>Jan 2020</td>
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<tr>
<td>NCT02757989</td>
<td>Allogeneic Hematopoietic Stem Cell Transplantation in Patients with Myelodysplastic Syndrome Low Risk</td>
<td>105</td>
<td>Apr 2021</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

References


**Billing Coding/Physician Documentation Information**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>38204</td>
<td>Management of recipient hematopoietic progenitor cell donor search and cell acquisition</td>
</tr>
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<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic</td>
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<tr>
<td>38207</td>
<td>Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage</td>
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<tr>
<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing</td>
</tr>
<tr>
<td>38209</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing</td>
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<tr>
<td>38210</td>
<td>Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion</td>
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<tr>
<td>38211</td>
<td>Transplant preparation of hematopoietic progenitor cells; tumor cell depletion</td>
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<td>38212</td>
<td>Transplant preparation of hematopoietic progenitor cells; red blood cell removal</td>
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<tr>
<td>38213</td>
<td>Transplant preparation of hematopoietic progenitor cells; platelet depletion</td>
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<td>38214</td>
<td>Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion</td>
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<td>38215</td>
<td>Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer</td>
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<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
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<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
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<td>38240</td>
<td>Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic</td>
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<td>86812</td>
<td>HLA typing; A, B, or C (eg, A10, B7, B27), single antigen</td>
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<td>86813</td>
<td>HLA typing; A, B, or C, multiple antigens</td>
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<td>86816</td>
<td>HLA typing; DR/DQ, single antigen</td>
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<td>86817</td>
<td>HLA typing; DR/DQ, multiple antigens</td>
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<td>86821</td>
<td>HLA typing; lymphocyte culture, mixed (MLC)</td>
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86822  HLA typing; lymphocyte culture, primed (PLC)
S2150  Bone marrow or blood-derived stem cells (peripheral or umbilical),
allogeneic or autologous, harvesting, transplantation, and related
complications; including: pheresis and cell preparation/storage; marrow
ablative therapy; drugs, supplies, hospitalization with outpatient follow-
up; medical/surgical, diagnostic, emergency, and rehabilitative services;
and the number of days of pre- and post-transplant care in the global
definition

ICD-10 Codes
C92.10-  Chronic myeloid leukemia, BCR/ABL-positive code range
C92.12  Atypical chronic myeloid leukemia, BCR/ABL-negative code range
C92.20-  Myelodysplastic disease, not classified
C92.22  Myeloproliferative disease, not classified
C94.6   Polycythemia vera
D45     Myelodysplastic syndromes code range
D46.0-  Other neoplasms of uncertain behavior of lymphoid, hematopoietic
D46.9   and related tissue code range
D47.0-  Myeloproliferative Neoplasms code range
D47.9   Other neoplasms of uncertain behavior of lymphoid, hematopoietic

Additional Policy Key Words
N/A

Policy Implementation/Update Information
12/1/01  New policy. Added to Surgery and Lab sections.
12/1/02  No policy statement change. Added new codes
12/1/03  No policy statement change.
12/1/05  No policy statement change. Removed from Lab section.
4/1/06   Considerations section revised to include general criteria.
12/1/06  No policy statement changes.
12/1/07  No policy statement changes.
12/1/08  “Myeloproliferative” added and “High-Dose Chemotherapy” removed
         from policy title and policy statements reworded, but the policy
         statements remain otherwise unchanged
12/1/09  Policy statements revised to indicate that RIC HSCT may be considered
         medically necessary as a treatment of myelodysplastic syndrome and
         myeloproliferative neoplasms in patients who for medical reasons would
         be unable to tolerate a myeloablative conditioning regimen. Term
         “Myeloproliferative Disorders” replaced with “Myeloproliferative
         Neoplasms” in title and text.
12/1/10  No policy statement changes.
12/1/11  No policy statement changes.
1/1/12   Coding updated.
12/1/12  No policy statement changes.
12/1/13  Minor changes in the description. Added to title name. No policy statement changes.

1/1/15  Reworded parts of policy statement, does not change the intent of the policy.

1/1/15  No policy statement changes.

1/1/16  No policy statement changes.

1/1/18  Changed “hematopoietic stem cell transplantation” to “hematopoietic cell transplantation” per NCCN terminology change. Policy statements unchanged.

1/1/19  No policy statement changes.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.