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Hematopoietic Cell Transplantation for Myelodysplastic Syndromes (MDS) and Myeloproliferative Neoplasms (MPN)

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Related Policies (if applicable)
SUR703.002: Hematopoietic Cell Transplantation (HCT) or Additional Infusion Following Preparative Regimens (General Donor and Recipient Information)
SUR703.041: Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia

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Coverage

Allogeneic hematopoietic cell transplantation (allo-HCT; HCT) **may be considered medically necessary** to treat myelodysplastic syndromes (MDS) in individuals when meeting the following criteria (Refer to the Description section for MDS categorization and risk for progression to leukemia):

- Increasing numbers of blasts, signaling a possible transformation to acute myeloid leukemia (AML). The following subtypes falling into this category are:
  - Refractory anemia with excess blasts;
  - Refractory anemia with excess blasts in transformation; or
  - Chronic myelomonocytic leukemia (CMML);
- Refractory anemia with or without ringed sideroblasts when chromosomal abnormalities are present or the disorder is associated with the development of significant cytopenias (e.g., neutrophils <500/mm^3, platelets <20,000/mm^3); OR
- Any of the following indications:

- Older age;
- International Prognostic Scoring System (IPSS) of intermediate-2 or high risk (see **Policy Guidelines** for the IPSS variables and outcome tables);
- Multiple comorbities (e.g., HCT-comorbidity index [HCT-CI] score higher than 2) (see **Policy Guidelines**);
- Red blood cell transfusion dependence;
- Neutropenia;
- Thrombocytopenia;
- High-risk cytogenetics; or
- Increasing blast percentage.

Allo-HCT **may be considered medically necessary** to treat myeloproliferative neoplasms (MPN) for individuals when meeting the following criteria (Refer to the Description section for MPN categorization and risk for progression to leukemia):

- Progression to myelofibrosis;
- Evolution toward acute leukemia;
- Essential thrombocythemia (ET) with an associated thrombotic or hemorrhagic disorder; OR
- Any of the following indications:
  - Cytopenias;
  - Transfusion dependence;
  - Increasing blast percentage over 5%; or
  - Age 60 to 65 years.

Allo-HCT **is considered experimental, investigational and/or unproven** for MDS or MPN that does not meet the criteria listed above.

Autologous HCT (auto-HCT) **is considered experimental, investigational and/or unproven** as a treatment of either MDS or MPN under any circumstance.

Policy Guidelines

Table PG 1. IPSS: Myelodysplastic Syndromes Prognostic Variables

Variable	0	0.5	1.0	1.5	2.0
Marrow blasts, %	<5	5 to 10	NA	11 to 20	21 to 30
Karyotype	Good	Intermediate	Poor	NA	NA
Cytopenias	0/1	2/3	NA	NA	NA

IPSS: International Prognostic Scoring System; NA: not applicable.

Table PG 2. IPSS: Myelodysplastic Syndromes Clinical Outcomes

Risk Group	Total Score	Median Survival, years	Time for 25% of patients to Progress to AML
Low	0	5.7	9.4 years
Intermediate-1	0.5 to 1.0	3.5	3.3 years
Intermediate-2	1.5 to 2.0	1.2	1.12 years
High	≥2.5	0.4	0.2 years

AML: acute myelocytic leukemia; IPSS: International Prognostic Scoring System.

Scoring system: A score from zero to two is determined for each of the three variables; the three values are added obtain the IPSS score. Thus, a patient with 12 percent bone marrow blasts (score 1.5), complex chromosomal changes (poor karyotype score 1), neutrophil count of 1000/microL, and platelet count of 50,000/microL (two cytopenias, score 0.5) would have an IPSS score of 3 (i.e., high risk).

Karyotype definitions:	Cytopenia definitions:
Good: Normal; -Y; del (5q); del (20q). *Poor*: Complex (≥3 abnormalities); abnormal chromosome 7. *Intermediate*: All others.	*Red blood cells*: Hemoglobin <10 g/dL (100 g/L). *White blood cells*: Absolute neutrophil count <1800/microL. *Platelets*: Platelet count <100,000/microL.

All individuals with intermediate-2 or high risk MDS, as calculated by the IPSS, should be offered the opportunity to discuss allo-HCT with a transplantation physician. The final decision on transplant eligibility should be made based on a risk-benefit assessment, and the needs and wishes of the individual.

HCT Comorbidity Index (HCT-CI)

The HCT-CI is a comorbidity index that comprises 17 different categories of organ dysfunction. Positive findings are summated into a total score. The HCT-CI provides information with regard to the overall as well as non-relapse mortality risk a patient is likely to experience after hematopoietic cell transplantation and it can only be used by experienced physicians in the context of other risk factors for mortality such as the degree of cancer severity and the type of transplant.

Description

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

Myelodysplastic Syndromes

MDS can occur as a primary (idiopathic) disease or can be secondary to cytotoxic therapy, ionizing radiation, or other environmental insults. 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 62% among individuals older than age 70 years. Patients succumb either 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 previously used to classify MDS into 5 subtypes:

1) Refractory anemia (RA);
2) Refractory anemia with ringed sideroblasts (RARS);
3) Refractory anemia with excess blasts (RAEB);
4) Refractory anemia with excess blasts in transformation (RAEBT); and
5) Chronic myelomonocytic leukemia (CMML).

The FAB system was supplanted by that of the World Health Organization (WHO), which differentiates between MDS defined by genetic abnormalities or by morphologic features (in the form of dysplastic cell lineages) and reduces the threshold maximum blast percentage for the diagnosis of MDS from 30% to 20%. (1)

The most commonly used prognostic scoring system for MDS is the 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 (e.g., peripheral blood counts, blast percentage). However, the IPSS has been useful in a 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. (2) This system stratifies patients into 5 categories: very poor, poor, intermediate, good, and very good. There has been an 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 (WPSS) uses a 6-category system, which allows more precise prognostication of overall survival (OS) duration, as well as risk for progression to AML.

Myeloid neoplasms are categorized according to criteria developed by the WHO. Neoplasms are risk-stratified using the International Prognostic Scoring System (IPSS).

Refer to the following for the **Myeloid Neoplasm Categorization**:

2022 WHO Classification Scheme for Myeloid Neoplasms and Histiocytic/Dendritic Neoplasms

- **Clonal hematopoiesis (CH)**
  - CH of indeterminate potential (CHIP);
  - Clonal cytopenia of undetermined significance (CCUS).
- **Myeloproliferative neoplasms (MPN)**
  - Chronic myeloid leukemia (CML), BCR-ABL1^{+};
  - Chronic neutrophilic leukemia (CNL);
  - Polycythemia vera (PV);
  - Primary myelofibrosis (PMF);
  - Essential thrombocythemia (ET);
  - Chronic eosinophilic leukemia;
  - MPN, not otherwise specified;
  - Juvenile myelomonocytic leukemia.
- **Mastocytosis**
  - Cutaneous mastocytosis;
  - Systemic mastocytosis;
  - Mast cell sarcoma.
- **Childhood MDS**
  - Childhood MDS with low blasts:
    - Hypocellular;
    - Not otherwise specified;
    - Childhood MDS with increased blasts.
- **Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (MLN-TK)**
- **Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)**
  - Chronic myelomonocytic leukemia (CMML);
  - MDS/MPN with neutrophilia;
  - MDS/MPN with *S32B1* mutation and thrombocytosis;
  - MDS/MPN, not otherwise specified.
- **Myelodysplastic syndromes (MDS)**
- MDS with defining genetic abnormalities;
  - MDS with low blasts and isolated 5q deletion (MDS-5q);
  - MDS with low blasts and *SF3B1* mutation (MDS-*SF3B1*), or MDS with low blasts and ring sideroblasts;
  - MDS with biallelic *TP53* inactivation (MDS-bi*TP53*).
- MDS, morphologically defined:
  - MDS with low blasts (MDS-LB);
  - MDS, hypoplastic (MDS-h);
  - MDS with increased blasts (MDS-IB):
    - MDS-IB1;
    - MDS-IB2;
    - MDS with fibrosis (MDS-f).
- **Acute myeloid leukemia (AML)**

- AMD with defining genetic abnormalities;
- AML, defined by differentiation.

- **Secondary myeloid neoplasms**
  - Myeloid neoplasms post cytotoxic therapy;
  - Myeloid neoplasms with germline predisposition.
- **Dendritic cell and histiocytic neoplasms**
  - Plasmacytoid dendritic cell neoplasms;
  - Langerhans cell and other dendritic cell neoplasms;
  - Histiocytic neoplasms.
- **Acute leukemias of ambiguous lineage (ALAL)**
  - ALAL with defining genetic abnormalities;
  - ALAL, immunophenotypically defined.
- **Genetic tumors with predisposition to myeloid neoplasia**

Risk Stratification of MDS

Risk stratification for MDS is performed using the IPSS (see Policy Guidelines). This system was developed after pooling data from 7 studies that used independent, risk-based prognostic factors. The prognostic model and the scoring system were 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 group patients into either low-risk or high-risk groups (see Policy Guidelines). The low-risk group includes low-risk and intermediate-1 IPSS groups; treatment goals in low-risk MDS patients are to improve quality of life and achieve transfusion independence. In the high-risk group, which includes intermediate-2 and high-risk IPSS groups, treatment goals are slowing disease progression to AML and improving survival. IPSS is usually calculated on diagnosis. The role of lactate dehydrogenase, marrow fibrosis, and β_2-microglobulin also should be considered after establishing IPSS. If elevated, the prognostic category worsens by 1 category change.

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. (2) This system stratifies patients into 5 categories: very poor, poor, intermediate, good, and very good. There has also been an investigation into using the 5-category IPSS to better characterize risk in MDS.

MDS Treatment

Treatment of non-progressing MDS has previously 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. An array of therapies are now available to treat MDS, including hematopoietic growth factors (e.g., erythropoietin, darbepoetin, granulocyte colony-stimulating factor), transcriptional-modifying therapy (e.g., U.S. Food and Drug Administration [FDA]-approved hypomethylating agents, nonapproved histone deacetylase inhibitors), immunomodulators (e.g., lenalidomide, thalidomide, antithymocyte globulin, cyclosporine A), low-dose chemotherapy (e.g., cytarabine), and allo-HCT. Given the spectrum of treatments available, the goal of therapy must be decided upfront

whether it is to improve anemia, thrombocytopenia, or neutropenia, to eliminate the need for RBC transfusion, to achieve complete remission, or to cure the disease.

Allo-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, approximately 8,400 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.

MPNs are characterized by the slow but progressive expansion of a clone of cells with the potential evolution into a blast crisis similar to AML. MPNs 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 variants that affects protein tyrosine kinases or related molecules. The unifying characteristic common to all MPN is effective clonal myeloproliferation resulting in peripheral granulocytosis, thrombocytosis, or erythrocytosis that is devoid of dyserythropoiesis, granulocytic dysplasia, or monocytosis.

MPN Classification

MPNs are a subdivision of myeloid neoplasms that includes 4 classic disorders: chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocytopenia (ET), and primary myelofibrosis (PMF). The WHO classification also includes chronic neutrophilic leukemia, chronic eosinophilic leukemia not otherwise specified, and MPN unclassifiable. In the 2016 classification, mastocytosis is no longer considered a subgroup of the myeloproliferative neoplasms due to its unique clinical and pathologic features.

MPN Treatment

In indolent, non-progressing 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 ET and PV, and intermediate- and high-risk PMF.

The FDA (2011) 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 compared with placebo. (3) The Randomized Study of Ruxolitinib Tablets Compared to Best Available Therapy in Subjects With Primary Myelofibrosis, Post-Polycythemia Vera-Myelofibrosis or Post-Essential Thrombocythemia Myelofibrosis (COMFORT-II trial [2013]) compared ruxolitinib with best available therapy in patients who had intermediate- and high-risk myelofibrosis, and demonstrated improvements in spleen volume and OS. (4) In a randomized trial comparing ruxolitinib with best available therapy (including antineoplastic agents, most commonly hydroxyurea, glucocorticoids) with no therapy for treatment of myelofibrosis, Harrison et al. (2012) reported improvements in spleen size and quality of life, but not OS. (5) In 2019, the FDA

also approved fedratinib (Inrebic®) for adults with intermediate-2 or high-risk primary or secondary myelofibrosis based on results from a double-blind, randomized, placebo-controlled trial that found improvement in spleen volume and myelofibrosis-related symptoms. (6)

Myeloablative allo-HCT has been considered the only potentially curative therapy, but because most patients are of advanced age with attendant comorbidities, its use is limited to those who can tolerate the often-severe treatment-related adverse events of this procedure. However, the use of reduced-intensity conditioning (RIC) of conditioning regimens for allo-HCT has extended the potential benefits of this procedure to selected individuals with these disorders.

Hematopoietic Cell Transplantation (HCT)

HCT is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow function and immune function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT; auto-HCT) or a donor (allogeneic HCT; allo-HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. 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 auto-HCT. In allo-HCT, immunologic compatibility between donor and patient is a critical factor for achieving a successful outcome. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. An acceptable donor will match the patient at all or most of the HLA loci.

<u>Conditioning for HCT</u>

Conventional Conditioning

The conventional ("classical") practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of the initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease (GVHD), which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of the bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

Reduced-Intensity Conditioning (RIC) Allogeneic HCT
RIC refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose MAC treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. RIC regimens range from nearly total myeloablative to minimally myeloablative with lymphoablation, with 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. In this policy, the term RIC will refer to all conditioning regimens intended to be nonmyeloablative.

Regulatory Status
The FDA regulates human cells or tissues intended for implantation, transplantation, infusion, or transfer into a human recipient through the Center for Biologics Evaluation and Research (CBER), under Code of Federal Regulation (CFR) title 21, parts 1270 and 1271. (56) Hematopoietic stem cells are included in these regulations.

Rationale

This policy was created in 2009 and has been updated with searches of the PubMed database. The most recent literature update was performed through November 15, 2022. While the coverage of this policy does not address myeloablative conditioning (MAC) or reduced intensity conditioning (RIC) prior to hematopoietic cell transplantation (HCT), discussion of HCT outcomes may be influenced by the type of preparative conditioning completed prior to the transplantation.

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the 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 1 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 (MDS)

Clinical Context and Therapy Purpose

The purpose of myeloablative (MAC) or reduced-intensity conditioning (RIC) allogeneic hematopoietic cell transplant (allo-HCT) in patients who have MDS is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with MDS.

Interventions

The therapies being considered are MAC or RIC allo-HCT.

Comparators

The following therapies are currently being used: standard of care.

Outcomes

The general outcomes of interest are mortality and morbidity. Beneficial outcomes are an improvement in overall survival (OS) and disease-specific survival (DSS). Harmful outcomes are treatment-related morbidity and mortality. Follow-up over months to years is of interest for relevant outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.

- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Myeloablative Conditioning Allo-HCT

Despite the successes seen with drugs now available to treat MDS (e.g., decitabine, azacitidine, lenalidomide), allo-HCT is the only treatment capable of complete and permanent eradication of the MDS clone. (7)

Systematic Review

A 2009 review of HCT for MDS evaluated the evidence for allo-HCT with MAC for MDS. (8) Reviewers selected 24 studies (prospective and retrospective) published between 2000 and 2008 that included a total 1378 cases (age range, 32 to 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 (CMML), 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 (BU) plus cyclophosphamide (CY) and CY plus total body irradiation (TBI), 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. The OS rates ranged from 25% at 2 years to 52% at 4 years, with non-relapse 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. (9) 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 (i.e., 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). (10) In a cohort of 903 patients retrospectively identified from the European Society for Blood and Marrow Transplantation (ESBMT) 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

Systematic Reviews

Song et al. (2021) evaluated the efficacy of RIC followed by allo-HCT in patients with AML and MDS via a meta-analysis of 6 RCTs (N=1413). (11) The 6 RCTs compared RIC to MAC before first allo-HCT in patients with AML in complete remission or MDS, had a median follow-up of >1 year, and displayed a low risk of bias. The primary endpoint was OS. Results revealed that OS was not significantly different between RIC and MAC (hazard ratio [HR], 0.95; 95% confidence interval [CI], 0.64 to 1.4; p=.80), with combined long-term follow-up data also showing no difference in OS between the 2 conditioning approaches (HR, 0.86; 95% CI, 0.53 to 1.41; p=.56). The cumulative incidence of relapse was also similar between the groups (HR, 1.18; 95% CI, 0.88 to 1.49; p=.28). Nonrelapse mortality was significantly improved with RIC as compared to total body irradiation/busulfan-based MAC (HR, 0.53; 95% CI, 0.36 to 0.8; p=.002); however, treosulfan-based MAC significantly reduced nonrelapse mortality as compared to RIC (HR, 1.67; 95% CI, 1.02 to 2.72; p=.04). RIC was associated with a trend of increasing graft failure (p=.06); however, graft failure in both arms was rare. The median duration of follow-up among the studies ranged from 12 to 119 months. The authors concluded that RIC is recommended as an adequate option of preparative treatment before allo-HCT for patients with AML in complete remission or MDS. Limitations of the meta-analysis included the small number of included clinical trials, significant heterogeneity between included studies for some outcomes, and lack of blinding in some studies.

Randomized Controlled Trials

No published randomized trials have compared RIC plus allo-HCT with conventional chemotherapy alone in patients with MDS and AML for whom MAC chemotherapy and allo-HCT are contraindicated.

Three RCTs all of which are included in the systematic review by Song et al. (2021) (11), have compared RIC and MAC regimens before allo-HCT in patients with MDS. (12-14) The RCTs are heterogeneous in patient characteristics and conditioning regimens and their findings vary based on these differences. In a long-term follow-up of one of the RCTs, (13) Scott et al. (2021) found that, at 4 years, transplant-related mortality was significantly increased with MAC as compared to RIC (25.1% vs. 9.9%; p<.001) and those who received RIC had a significantly increased relapse risk (HR, 4.06; 95% CI, 2.59 to 6.35; p<.001). (15) Among those who relapsed after HCT, post-relapse survival was similar between groups at 3 years (24% for MAC vs. 26% for RIC). Patients administered MAC had superior OS (HR, 1.54; 95% CI, 1.07 to 2.2; p=.03).

Overall, findings from these RCTs appear consistent with the American Society for Blood and Marrow Transplantation's (2009) systematic review (previously described), which 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." (9) Other reviews (2010 to 2012) have also drawn conclusions similar to those of the American Society for Blood and Marrow Transplantation. (16-21) Given the absence of curative therapies for these patients, RIC allo-HCT may be considered as a risk-adapted treatment strategy for patients with MDS who could benefit from allo-HCT but who are at high-risk of MAC regimen intolerance.

Noncomparative and Observational Studies

Additional nonrandomized evidence includes uncontrolled studies and prospective and retrospective cohort studies. Evidence from a number of largely heterogeneous, uncontrolled studies of RIC with allo-HCT has shown long-term remission (i.e., >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. (8, 22-32) 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 a relapse risk of 6% to 61%. Rates of OS ranged between 44% at 1 year and 46% at 5 years (median follow-up range, 14 months to >4 years).

In general, nonrandomized studies of RIC compared to MAC showed a low rate of engraftment failure and low non-relapse mortality with RIC, but a higher relapse rate than with MAC allo-HCT. 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. (33) 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 the 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 to 69 years) with advanced MDS (refractory anemia with excess blasts or refractory anemia in transformation). (34) 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 to 59 years; 47% for RIC vs 47% for MAC; p=.001), and less likely to receive an unrelated donor transplant (54% vs 70%; p=.001). Three-year OS rates did not differ between groups (44.1% for RIC vs 42.7% for MAC; p=.330). Although patients treated with RIC had a significantly lower 3-year cumulative incidence of NRM (25.6% vs 37.9%; p=.002), they had a significantly higher 3-year incidence of relapse than patients treated with MAC (29.9% vs 22.8%; p=.029).

Kim et al. (2012) published a phase 3 randomized trial (N=83 patients) comparing toxicity rates for 2 conditioning regimens (reduced CY, fludarabine, and anti-thymocyte globulin [ATG]; standard CY-ATG). (35) 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=.003). Subgroup analyses showed no differences in the overall results based on differential diagnosis.

Outcomes After Allo-HCT in Mixed MDS Populations

Noncomparative and Observational Studies

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

Study	Patient Population	Type of HCT	Summary of Outcomes
Basquiera et al. (2015) (36)	52 pediatric patients with MDS	• Allo-HCT (59% with related donors) • Stem cell source: ○ Bone marrow, 63% ○ Peripheral blood, 26% ○ Umbilical cord blood, 11%	• 5-y DFS=50% • 5-y OS=55%
Boehm et al. (2014) (37)	60 adults with MDS or secondary AML	• Allo-HCT • MAC in 36 patients; RIC in 24 patients	10-y OS=46%
Damaj et al. (2014) (38)	128 adults with MDS: 40 received AZA before HCT and 88 who received BSC	RIC allo-HCT	• 3-y OS=53% in AZA group vs 53% in BSC group (p=.69) • 3-y RFS=37% in AZA group vs 42% in BSC group (p=.78) • 3-y NRM=20% in AZA group vs 23% in BSC group (p=.74)
Di Stasi et al. (2014) (39)	227 patients with MDS or AML	• Allo-HCT • Donor source: ○ Matched-related, 38% ○ Matched-unrelated, 48% ○ Haploidentical, 14%	3-y PFS for patients in remission: • 57% for matched-related • 45% for matched-unrelated • 41% for haploidentical (p=.417)
Onida et al. (2014) (40)	• 523 patients with MDS • IPSS cytogenic risk group: ○ Good risk: 53.5% ○ Intermediate risk: 24.5% ○ Poor risk: 22%	• Allo-HCT • RIC in 12%	5-y OS based on IPSS cytogenic risk group: • Good risk: 48% • Intermediate risk: 45% • Poor risk: 30%
Oran et al. (2014) (41)	• 256 patients with MDS • Pretreatment:	• Allo-HCT • RIC in 36.7%	3-y EFS based on cytoreductive therapy:

	○ No cytoreductive Chemotherapy: 30.5% ○ Chemotherapy: 15.6% ○ HMA: 47.7% ○ Chemotherapy + HMA: 6.2%		• No cytoreductive chemotherapy: 44.2% • Chemotherapy: 30.6% • HMA: 34.2% • Chemotherapy + HMA: 32.8% (p=.50)
Yoshimi et al. (2014) (42)	17 children with secondary MDS or AML after childhood aplastic anemia	• Allo-HCT	5-y OS and EFS=41%
Basquiera et al. (2015) (43)	• 84 adults with MDS Cytogenic risk group: ○ Standard: 65.5% ○ Adverse: 12.6% ○ Unknown: 21.9%	• Allo-HCT • RIC in 31.1%	OS: • Median: 23.5 mo (95% CI, 1.7 to 45.3 mo) • 1-y=61% (95% CI, 50% to 70%) • 4-y=38% (95% CI, 27% to 49%) PFS: • Median: 19.9 mo (95% CI, 9 to 31 mo) • 1-y=57% (95% CI, 46% to 67%) • 4-y=37% (95% CI, 26% to 48%)
Symeonidis et al. (2015) (44)	• 513 adults with CMML • Pretreatment: ○ No prior DMT: 28% ○ DMT: 72%	• Allo-HCT • RIC in 41.6%	• 1-y NMR=31% • 4-y NRM=41% • 4-y RFS=27% • 4-y OS=33%
Pohlen et al. (2016) (45)	• 187 patients with refractory AML (87%) or high- risk MDS (13%)	• Allo-HCT • RIC in 52% • Unrelated donors in 73% • Stem cell source: ○ Bone marrow, 6% ○ Peripheral blood, 94%	• 3-y RFS=32% (95% CI, 25% to 39%) • 3-y OS=35% (95%CI, 27% to 42%)
Heidenreich et al. (2017) (46)	• 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%

Robin et al. (2022) (47)	• 114 adults with CMML age 18 to 70 years
	• CMML Prognosis Scoring System risk:
	  ○ Low: 20%
	  ○ Intermediate-1: 31%
	  ○ Intermediate-2: 40%
	  ○ High: 9%
	• Underwent allo-HCT: 43%
	• Transformed to AML prior to allo-HCT: 10%
		• MAC or RIC allo-HCT; details of intensity and donor source not reported	• 5-y OS:
			  ○ Lower-risk disease: 20% with allo-HCT vs. 42% without allo-HCT (p<0.001)
			  ○ Higher-risk disease: 27% with allo-HCT vs. 15% without allo-HCT (p=0.13)
			• Multivariate analyses of risk of death within 2 years and after 2 years:
			  ○ Lower-risk disease: Increased risk of death within 2 years with allo-HCT (HR=3.19); no difference in long-term survival after 2 years (HR-0.98)
			  ○ Higher-risk disease: Increased risk of death within 2 years with allo-HCT (HR=1.46); no difference in long-term survival after 2 years (HR=0.60)
			• Conditioning regimen and donor type were not associated with post-transplant survival (data not reported)

Allo: allogeneic; AML: acute myelogenous leukemia; AZA: azacitidine; BSC: best supportive care; chemo: chemotherapy; CMML: chronic myelomonocytic leukemia; DFS: disease-free survival; DMT: disease-modifying therapy; HR: hazard ratio; MA: hypomethylating agents; HCT: hematopoietic cell transplantation; IPSS: International Prognostic Scoring System; MA: myeloablative; MAC: myeloablative conditioning; MDS: myelodysplastic syndrome; NRM: non-relapse mortality; OS: overall survival; PFS: progression-free survival; RIC: reduced-intensity conditioning; RFS: relapse-free survival; y: year; mo: month.

Section Summary: MDS

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. Evidence from randomized and nonrandomized comparisons has suggested that RIC may be used as a risk-adapted strategy in high-risk 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 (MPN)

Clinical Context and Therapy Purpose

The purpose of MAC and RIC allo-HCT in patients who have MPN is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals who have MPN.

Interventions

The therapies being considered are MAC or RIC allo-HCT.

Comparators

The following therapies are currently being used: standard of care.

Outcomes

The general outcomes of interest are mortality and morbidity. Beneficial outcomes are an improvement in OS and DSS. Harmful outcomes are treatment-related morbidity and mortality. Follow-up over months to years is of interest for relevant outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Data on therapy for MPN are sparse. (29, 48, 49) As outlined in this medical policy, 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.

Systematic Reviews

Bewersdorf et al. (2021) assessed the available evidence on the efficacy and safety of allo-HCT in patients with myelofibrosis in a systematic review involving 43 studies (N=8739). (50) The analysis included 38 retrospective, 1 prospective, and 4 phase II clinical trials. Conditioning regimens used were variable with only 3 and 14 studies using exclusively MAC or RIC regimens, respectively. Additionally, donor sources and pre-transplantation treatment histories differed considerably among studies. The co-primary outcome was 1-, 2-, and 5-year OS. Rates of non-relapse mortality, RFS or progression-free survival (PFS), and safety were also evaluated. Regarding survival, 1-year, 2-year, and 5-year OS rates were 66.7% (95% CI, 63.5% to 69.8%), 64.4% (95% CI, 57.6% to 70.6%), and 55% (95% CI, 51.8% to 58.3%), respectively. Non-relapse mortality rates for the same time periods were 25.9% (95% CI, 23.3% to 28.7%), 29.7% (95% CI, 24.5% to 35.4%), and 30.5% (95% CI, 25.9% to 35.5%). Rates of 1-, 2- and 5-year RFS were 65.3% (95% CI, 56.5% to 73.1%), 56.2% (95% CI, 41.6% to 69.8%), and 53.6% (95% CI, 39.9% to 66.9%), respectively. PFS rates were 56.9% (95% CI, 41.4% to 71.2%), 50.6% (95% CI, 39.7% to 61.4%), and 43.5% (95% CI, 31.9% to 55.8%) for these same time periods. Acute GVHD was reported in 44% of patients, with chronic GVHD occurring in 46.5% of patients. The combined rate of graft failure was 10.6% (95% CI, 8.9% to 12.5%). Overall, the quality of the evidence was limited by the absence of RCTs and the retrospective design of most studies. Additionally, patient and transplant characteristics were variable among the included studies leading to moderate to substantial heterogeneity in the analyses.

Noncomparative and Observational Studies

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 (CIBMTR). (51) Median age was 47 years (range, 18 to 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. Rates of DFS for patients receiving RIC allo-HCT were comparable: 39% for HLA-identical sibling donors and 17% for unrelated donors at 3 years. In this large retrospective series, allogeneic transplantation for myelofibrosis resulted in long-term RFS in about one-third of patients.

The significant toxicity of MAC plus allo-HCT in MPN has led to study of RIC regimens for these diseases. Data from a direct, prospective comparison of outcomes of MAC and allo-HCT versus RIC and allo-HCT 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 a RIC regimen of low-dose (2 Gray) total body irradiation alone with or without fludarabine. (27) At a median follow-up of 47 months, 3-year RFS was 37%, 3-year OS was 43%, and 3-year NRM was 32%.

A 2009 retrospective study analyzed the impact of conditioning intensity on outcomes for allo-HCT in patients with myelofibrosis. (52) 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 to 60 years) underwent MAC and 23 patients (median age, 54 years; range, 38 to 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 to 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% to 62%] vs 43% [range, 35% to 76%], respectively; p=.11); there was a similar trend in the 3-year OS rate (68% [range, 45%-84%] vs 48% [range, 27% to 66%], respectively; p=.08). NRM rates at 3 years trended higher in MAC cases (48%; range, 31% to 74%) than in RIC cases (27%; range, 14% to 55%; p=.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.

Section Summary: MPN

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. Primarily, 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 myelodysplastic syndromes (MDS) who receive myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC) allogeneic hematopoietic cell transplantation (allo-HCT), the evidence includes systematic reviews, randomized controlled trials (RCTs), and numerous case series, which are often heterogeneous in terms of diseases included. Relevant outcomes are overall survival (OS), 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 OS of 40% to 50% are typical. Evidence from randomized

and nonrandomized comparisons has suggested that RIC may be used as a risk-adapted strategy in high-risk patients who are older and with more comorbidities without significantly worsening OS. RIC appears to be associated with lower rates of non-relapse mortality but higher cancer relapse than MAC HCT. At present, HCT is the only potentially curative treatment option for patients with MDS. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have MPN who receive MAC or RIC allo-HCT, the evidence includes a systematic review and retrospective observational series. Relevant outcomes are OS, disease-specific survival, and treatment-related mortality and morbidity. Evidence has suggested that RIC may be used as a risk-adapted strategy in high-risk patients who are older and have more comorbidities without significantly worsening OS. RIC appears to be associated with lower rates of non-relapse mortality but higher cancer relapse than myeloablative HCT. At present, HCT is the only potentially curative treatment option for patients with MPN. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

A search of peer reviewed literature identified no additional published studies, clinical trials or practice guidelines for the use of autologous HCT to treat MDS and MPN that would prompt reconsideration of the experimental, investigational and/or unproven coverage statement, which remains unchanged.

Practice Guidelines and Position Statements: MDS and MPN

National Comprehensive Cancer Network (NCCN)

Current NCCN clinical guidelines for myelodysplastic syndromes (v.1.2023) make the following general recommendation about allogeneic hematopoietic cell transplantation (allo-HCT) (53):

"For patients who are transplant candidates, an HLA [human leukocyte antigen]-matched sibling or HLA-matched unrelated donor can be considered. 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 myelodysplastic syndromes are outlined in Table 2. (53)

Table 2. Guidelines for Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes

Prognostic Category	Recommendations for Allo-HCT
IPSS low/intermediate-1 *OR* IPSS-R very low, low, intermediate *OR* WPSS very low, low, intermediate.	• Consider allo-HCT for select patients who have clinically relevant thrombocytopenia or neutropenia, 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 or lower serum erythropoietin level with inadequate response to erythropoietin stimulating agents and/or lenalidomide, with poor probability of or inadequate response/intolerance to immunosuppressive therapy, and no response or intolerance to azacitidine/decitabine or immunosuppressive therapy. • Consider allo-HCT for patients who have symptomatic anemia with del(5q), with inadequate response/intolerance to lenalidomide and/or erythropoietin stimulating agents, 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.

allo: allogeneic; HCT: hematopoietic cell transplantation; IPSS: International Prognostic Scoring System; WPSS: WHO Classification-based Prognostic Scoring System.

Table 3 summarizes the NCCN recommendations (v.3.2022) on the use of allo-HCT for the treatment of MPN. (54) 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 Allogeneic Hematopoietic Cell Transplantation for Myeloproliferative Neoplasms

Prognostic Category	Recommendations for Allo-HCT
Lower-risk myelofibrosis: MIPSS-70≤3 MIPSS-70+ Version 2.0 ≤3 DIPSS-Plus≤1 DIPSS≤2 MYSEC-PM <14	• In symptomatic patients with disease progression despite treatment with ruxolitinib, peginterferon alfa-2a, and/or hydroxyurea (if cytoreduction would be symptomatically beneficial), consider allo-HCT immediately or bridging therapy 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.
Higher-risk myelofibrosis: MIPAA-70 ≥4 MIPAA-70+ Version 2.0 ≥4 DIPSS-Plus >1 DIPSS>2 MYSEC-PM ≥14	• Consider allo-HCT immediately or bridging therapy can be used to decrease marrow blasts to an acceptable level prior to transplant. • Evaluation for allo-HCT is recommended for all patients.
Disease progression to advanced-stage/AML	• Induce remission with hypomethylating agents ± JAK inhibitors or intensive induction chemotherapy followed by allo-HCT.

allo: allogeneic; AML: acute myeloid leukemia; DIPSS: Dynamic International Prognostic Scoring System; HCT: hematopoietic cell transplantation; JAK: Janus kinase; MIPSS: Mutation-Enhanced International Prognostic Scoring System; MYSEC-PM: Myelofibrosis Secondary to PV (polycythemia vera) and ET (essential thrombocythemia)-Prognostic Model.

American Society of Transplantation and Cellular Therapy

In 2020, the American Society of Transplantation and Cellular Therapy (formerly The American Society for Blood and Marrow Transplantation) published updated guidelines on indications for HCT and immune effector cell therapy based on the recommendations of a multiple-stakeholder task force. (55) Table 4 summarizes categorizations for allo-HCT.

Table 4. Recommendations for the Use of HCT to Treat MDS, Myelofibrosis, and MPN

Indication	Recommendation
Myelodysplastic Syndromes	
Low/intermediate-1 risk	Standard of care, clinical evidence available (large clinical trials and observational studies are not available; however, sufficiently large cohort studies have shown efficacy with "acceptable risk of morbidity and mortality")
Intermediate-2/high-risk	Standard of care ("well defined and generally supported by evidence in the form of high-quality clinical trials and/or observational studies")
Myelofibrosis and Myeloproliferative Neoplasms	
Primary, low risk	Standard of care ("well defined and generally supported by evidence in the form of high-quality clinical trials and/or observational studies")
Primary, intermediate/high risk	Standard of care ("well defined and generally supported by evidence in the form of high-quality clinical trials and/or observational studies")
Secondary	Standard of care ("well defined and generally supported by evidence in the form of high-quality clinical trials and/or observational studies")

Hypereosinophilic syndromes, refractory	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")

HCT: hematopoietic cell transplantation; MDS: myelodysplastic syndromes; MPN: myeloproliferative neoplasms.

Ongoing and Unpublished Clinical Trials

Some currently ongoing trials that might influence this policy are listed in Table 5.

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01760655	Reduced Intensity Conditioning Before Donor Stem Cell Transplant in Treating Patients with High-Risk Hematologic Malignancies	72	Sep 2022 (last update posted Sep 2021)
NCT02757989	Allogeneic Hematopoietic Stem Cell Transplantation in Patients with Myelodysplastic Syndrome Low Risk	79	Jun 2024
NCT05367583	Cohort Study Assessing the Treatment Strategy for High-Risk Myelodysplastic Syndromes in Patients Under 70 (COMYRE)	107	Oct 2024

NCT: national clinical trial; No.: Number.

[a]: Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	36511, 38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38220, 38221, 38222, 38230, 38232, 38240, 38241, 38242, 38243, 81265, 81266, 81267, 81268, 81370, 81371, 81372, 81373, 81374, 81375, 81376, 81377, 81378, 81379, 81380, 81381, 81382, 81383, 86805, 86806, 86807, 86808, 86812, 86813, 86816, 86817, 86821, 86822, 86825, 86826, 86828, 86829,

	86830, 86831, 86832, 86833, 86834, 86835, 86849, 86950, 86985, 88240, 88241
HCPCS Codes	S2140, S2142, S2150

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
11/01/2023	Document updated with literature review. Coverage unchanged. References 1, 47, and 54 added; some updated and others removed.
05/15/2022	Document updated with literature review. Coverage unchanged. References 5, 10, 14, 48, and 53 added; some updated and others removed.
08/01/2021	Reviewed. No changes.
11/01/2020	Document updated with literature review. The following changes were made to the Coverage section: 1. The medically necessary statement for allogeneic hematopoietic cell transplantation (allo-HCT; HCT) to treat myelodysplastic syndromes (MDS) includes older age and Multiple comorbities (e.g., HCT-

	comorbidity index [HCT-CI] score higher than 2) under any of the following indications. 2. NOTE 4 was added to define the HCT-CI. References 9-11 and 54 were added and others revised.
09/15/2019	Reviewed. No changes.
05/15/2018	Document updated with literature review. Coverage unchanged. References 38-39 and 49-50, 52 added.
06/01/2017	Reviewed. No changes.
10/15/2016	Document updated with literature review. The following was added to the allogeneic hematopoietic stem-cell transplantation medically necessary criteria for increasing number of blasts: "Refractory anemia with excess blasts; Refractory anemia with excess blasts in transformation; or Chronic myelomonocytic leukemia (CMML). The following NOTEs and Tables were added to coverage: 1) International Prognostic Scoring System (IPSS) Variables and Outcome information for myelodysplastic syndromes (MDS); 2) Karotype definitions; and 3) Cytopenia definitions.
07/15/2015	Document updated with literature review. The following was added to the medically necessary criteria for myelodysplastic syndromes: "In patients with any of the following indications: International Prognostic Scoring System of intermediate-2 or high risk; Red blood cell transfusion dependence, neutropenia; Neutropenia; Thrombocytopenia; High-risk cytogenetics; or Increasing blast percentage." The following was added to the medically necessary criteria for myeloproliferative neoplasms: "When there are any of the following indications: Cytopenias; Transfusion dependence; Increasing blast percentage over 5%; or Age 30 to 65 years." The following coverage statement was added: "Allogeneic HSCT is considered experimental, investigational and/or unproven for myelodysplastic syndrome or for myeloproliferative neoplasm that does not meet the criteria listed above." Title changed from Stem-Cell Transplant for Myelodysplastic Syndromes (MDS) and Myeloproliferative Neoplasms (MPN).
06/01/2014	Document updated with literature review. The following was changed: 1) Expanded coverage to consider a) donor leukocyte infusion (DLI) and hematopoietic progenitor cell (HPC) boost as medically necessary for myelodysplastic syndromes and myeloproliferative neoplasms that has relapsed, to prevent relapse in the setting of a high-risk relapse, or to convert a patient from mixed to full donor chimerism; b) DLI and HPC boost are considered experimental, investigational and/or unproven following an AlloSCS treatment for MDS/MPN that was originally considered experimental, investigational and/or unproven for the treatment of MDS/MPN OR as a treatment prior to AlloSCS; and, 2) Expanded coverage to consider a) short tandem repeat (STR) markers medically necessary when used in pre- or post-stem-cell support testing of the donor and recipient DNA profiles as a way to assess the status of donor cell engraftment following AlloSCS for MDS/MPN; b) all other uses of STR markers MDS and MPN

	experimental, investigational and/or unproven, if not listed in the coverage section**.** Description and Rationale were significantly changed, including the 2008 World Health Organization Classification and International Prognostic Scoring System. Title changed from Stem-Cell Transplant for Myelodysplastic Syndromes and Myeloproliferative Diseases.
04/01/2010	New medical document originating from: SUR703.017, Peripheral/Bone Marrow Stem-Cell Transplantation (PSCT/BMT) for Non-Malignancies; SUR703.018, Peripheral/Bone Marrow Stem-Cell Transplantation (PSCT/BMT) for Malignancies; SUR703.022, Cord Blood as a Source of Stem-Cells (CBSC); SUR703.023, Donor Leukocyte Infusion (DLI); and SUR703.024, Tandem/Triple High-Dose Chemoradiotherapy with Stem-Cell Support for Malignancies. Stem-Cell transplant continues to be medically necessary when stated criteria are met. [NOTE: A link to the medical policies with the following titles can be found at the end of the medical policy SUR703.002, Stem-Cell Reinfusion or Transplantation Following Chemotherapy (General Donor and Recipient Information): • Peripheral/Bone Marrow Stem-Cell Transplantation (PSCT/BMT) for Non-Malignancies; • Peripheral/Bone Marrow Stem-Cell Transplantation (PSCT/BMT) for Malignancies; • Cord Blood as a Source of Stem-Cells; • Donor Leukocyte Infusion (DLI); and • Tandem/Triple High-Dose Chemoradiotherapy with Stem-Cell Support for Malignancies.