Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Title: Bone Marrow Transplant Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms, Allogeneic

Description/Background

MYELODYSPLASTIC SYNDROMES

Myelodysplastic syndromes (MDS) are a group of rare cancers that affect the bone marrow and disrupt the production of blood cells. Immature blood cells in the marrow do not mature into healthy cells. These immature cells remain in the marrow causing the bone marrow to reduce the amount of blood cells it creates. Fewer healthy blood cells lead to infection, anemia and bleeding. Some types of MDS (see below) have no known cause while others occur in response to cancer treatments or chemical exposure.

Myelodysplastic syndromes (MDS) can occur as a primary (idiopathic) disease or can be secondary to cytotoxic therapy, ionizing radiation, or other environmental insult. Chromosomal abnormalities are seen in 40% to 60% of patients, frequently involving deletions of chromosome 5 or 7, or an extra chromosome as in trisomy 8. Most MDS diagnoses occur in individuals older than age 55 to 60 years, with an age-adjusted incidence of 62% among individuals older than age 70 years. Patients succumb either to disease progression to acute myeloid leukemia (AML) or to complications of pancytopenias. Individuals with higher blast counts or complex cytogenetic abnormalities have a greater likelihood of progressing to AML than do other patients.

Myelodysplastic Syndrome Classification and Prognosis

The French-American-British system was previously used to classify MDS into 5 subtypes: 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 French-American-British 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 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 (e.g., 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.(1) 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 uses a 6-category system, which allows more precise prognostication of overall survival (OS) duration, as well as risk for progression to AML.

Myelodysplastic Syndrome Treatment

Treatment of non-progressing MDS has previously involved best supportive care, including red blood cell 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., Food and Drug Administration–approved hypomethylating agents, nonapproved histone deacetylase inhibitors), immunomodulators (e.g., lenalidomide, thalidomide, antithymocyte globulin, cyclosporine A), low-dose chemotherapy (e.g., cytarabine), and allogeneic hematopoietic cell transplantation (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 red blood cell 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 preference, risk category, and severity of MDS at presentation. Allo-HCT is discussed in more detail in a subsequent section.

CHRONIC MYELOPROLIFRATIVE NEOPLASMS

Myeloproliferative neoplasms (MPN) are a group of blood cancers where the bone marrow uncontrollably overproduces red and white blood cells, and/or platelets. Usually 1 type of blood cell is dominantly mass produced; however there are occasions when the body will overproduce multiple types of blood cells. Classification of an MPN is dependent on the type of blood cell(s) being overproduced. When too many white blood cells are produced, MPN will progress to acute leukemia. Chronic MPN usually occur sporadically; however, familial clusters of MPN have been reported.

Chronic myeloproliferative neoplasms are clonal bone marrow stem cell disorders; as a group, approximately 8400 MPN are diagnosed annually in the United States. Like MDS, MPN

primarily occur in older individuals, with approximately 67% reported in patients aged 60 years and older.

MPN are characterized by the slow but progressive expansion of a clone of cells with the potential evolution into a blast crisis similar to AML. MPN share a common stem cell–derived clonal heritage, with phenotypic diversity attributed to abnormal variations in signal transduction as the result of a spectrum of 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.

Myeloproliferative Neoplasm Classification
Myeloproliferative neoplasms (MPN) are a subdivision of myeloid neoplasms that includes 4 classic disorders: chronic myeloid leukemia, polycythemia vera, essential thrombocytopenia, and primary myelofibrosis. 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.

Myeloproliferative Neoplasm 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.

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 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.(4) In a randomized trial comparing ruxolitinib to best available therapy, including antineoplastic agents, most commonly hydroxyurea, glucocorticoids, and no therapy, for myelofibrosis, Harrison et al (2012) demonstrated 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, use of reduced-intensity conditioning (RIC) for allo-HCT has extended the potential benefits of this procedure to selected individuals with these disorders.

HEMATOPOIETIC CELL TRANSPLANTATION
HCT is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow 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) or a donor (allo-HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allogeneic stem cell transplant, immunologic compatibility between donor and patient is critical for achieving a successful outcome. Compatibility is established by typing of human leukocyte antigen (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.

CONDITIONING FOR HEMATOPOIETIC CELL TRANSPLANTATION

Myeloablative (Conventional) Conditioning

The myeloablative (conventional) practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation. Intense conditioning regimens are limited to individuals whose health status is sufficient to tolerate the administration of cytotoxic agents with 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 initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self-immunologic effector cells. While the slower GVM effect is considered the potentially curative component, it may be overwhelmed by substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host-disease, 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 individual before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the individuals disease is in complete remission. Individuals who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

Reduced-Intensity or Non-myeloablative Conditioning for Allo-HCT

Reduced-intensity conditioning (RIC) sometimes referred to as non-myloablative (NMA)-conditioning, refers to the pretransplant use of lower doses of cytotoxic drugs with or without less intense regimens of radiotherapy than are used in myeloablative conditioning treatments. Although the definition of RIC/NMA 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/NMA 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. These RIC/NMA regimens range from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and individual condition. Individuals who undergo

RIC/NMA with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism.

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 (CFR) Title 21, parts 1270 and 1271. Hematopoietic cells are included in these regulations.

Medical Policy Statement

The safety and effectiveness of allogeneic HCT has been established as a treatment of myelodysplastic syndromes or myeloproliferative neoplasms. It is a useful therapeutic option for individuals meeting selection criteria.

Inclusionary and Exclusionary Guidelines

Inclusions:
Allogeneic[a] HCT may be considered established as a treatment for one of the following:
- Myelodysplastic syndromes
- Myeloproliferative neoplasms.

[a] *Includes myeloablative, RIC and nonmyeloablative regimens*

Exclusions:
Individuals not meeting the above diagnostic criteria.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

38204	38205	38207	38208	38209	38210
38211	38212	38213	38214	38215	38230
38240	38242	38243	81265	81266	81267
81268	81370	81371	81372	81373	81374
81375	81376	81377	81378	81379	81380
81381	81382	81383	86812	86813	86816
86817	86821	S2140	S2142	S2150	

Other codes (investigational, not medically necessary, etc.):

N/A

POTENTIAL CONTRAINDICATIONS FOR TRANSPLANT:

Note: Final patient eligibility for transplant is subject to the judgment and discretion of the requesting transplant center.

The selection process for approved tissue transplants is designed to obtain the best result for each patient. Therefore, potential contraindications to HCT may include, but are not limited to:

- Poor cardiac function: Ejection fraction should be greater than 45% with no overt symptoms of congestive heart failure.
- Poor pulmonary function: Pulmonary function tests should be greater than or equal to 50% of predicted value.
- Poor renal function: Renal creatinine clearance should be greater than 40 ml/min or creatinine must be less than or equal to 2mg/dl.
- Poor liver function: There should be no history of severe chronic liver disease
- Presence of HIV or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus (HTLV-1).

Clinical documentation supplied to the health plan must demonstrate that attending staff at the transplant center have considered all contraindications as part of their overall evaluation of potential organ transplant recipients and have decided to proceed.

Policy Guidelines

MYELOID NEOPLASMS

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

2022 WHO Classification Scheme for Myeloid Neoplasm 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
  - Primary myelofibrosis (PMF)
  - Essential thrombocythemia
  - 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 SF3B1 mutation and thrombocytosis
  - MDS/MPN, not otherwise specified
- *Myelodysplastic neoplasms (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-biTP53)
  - 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)*
  - AML with defining genetic abnormalities
  - AML, defined by differentiation
- *Secondary myeloid neoplasms*
  - Myeloid neoplasms post cytotoxic therapy
  - Myeloid neoplasms associated 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 tumor syndromes with predisposition to myeloid neoplasia*

Risk Stratification of MDS

Risk stratification for MDS is performed using the IPSS (see Table PG1). 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 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 group individuals into either low-risk or high-risk groups (see Table PG2). The low-risk group includes low-risk and intermediate-1 IPSS groups; treatment goals in low-risk MDS individuals 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 acute myeloid leukemia (AML) and improving survival. IPSS is usually calculated on diagnosis. The role of lactate dehydrogenase, marrow fibrosis, and β2-microglobulin also should be considered after establishing IPSS. If elevated, the prognostic category worsens by 1 category change.

Table PG1. International Prognostic Scoring System: Myelodysplastic Syndrome Prognostic Variables

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

IPSS: International Prognostic Scoring System.

Table PG2. IPSS: Myelodysplastic Syndrome Clinical Outcomes

Risk Group	Total Score	Median Survival, y	Time for 25% of patients to Progress to AML
Low	0	5.7	9.4 years
Intermediate-1	0.5-1.0	3.5	3.3 years
Intermediate-2	1.5-2.0	1.2	1.12 years
High	³2.5	0.4	0.2 years

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

An updated 5-category IPSS has been proposed for prognosis in individuals 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 also been investigation into using the five-category IPSS to better characterize risk in MDS.

Given the long natural history of MDS, allogeneic hematopoietic cell transplantation (allo-HCT) is typically considered in individuals with increasing numbers of blasts, signaling a possible transformation to AML. Subtypes falling into this category include refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, or chronic myelomonocytic leukemia.

Individuals with refractory anemia with or without ringed sideroblasts may be considered candidates for allo-HCT 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).

Individuals with MPN may be considered candidates for allo-HCT when there is progression to myelofibrosis or evolution toward acute leukemia. In addition, allo-HCT may be considered in individuals with essential thrombocythemia with an associated thrombotic or hemorrhagic disorder. Use of allo-HCT should be based on cytopenias, transfusion dependence, increasing blast percentage over 5%, and age.

Some individuals for whom a conventional myeloablative allo-HCT could be curative may be candidates for reduced-intensity conditioning (RIC) allo-HCT. These include individuals whose age (typically >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 (MAC) regimen. The ideal allogeneic donors are human leukocyte antigen (HLA)—identical siblings, matched at the HLA-A, -B, and -DR loci (6/6). Related donors mismatched at 1 locus are also considered suitable donors. A matched, unrelated donor 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 individual, who usually share only 3 of the 6 major histocompatibility antigens. Most individuals will have such a donor; however, the risk of graft-versus-host disease (GVHD) and overall morbidity of the procedure may be severe, and experience with these donors is not as GVHD extensive as that with matched donors.

Evidence and clinical guidelines suggests RIC allo-HCT may be considered as a risk-adapted strategy for high-risk individuals of MAC-intolerance as follows:

MDS
- Older age
- IPSS intermediate-2 or high risk
- Multiple comorbidities (e.g., hematopoietic cell transplantation-comorbidity index (HCT-CI) score higher than 2
- Red blood cell transfusion dependence
- Neutropenia
- Thrombocytopenia
- High-risk cytogenetics
- Increasing blast percentage

Myeloproliferative neoplasm
- Cytopenias
- Transfusion dependence
- Increasing blast percentage over 5%
- Age 60 to 65 years.

Rationale

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 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.

MYELODYSPLASTIC SYNDROMES

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

The following PICOs were used to select literature to inform this review.

Populations
The relevant population of interest are individuals with myelodysplastic syndromes.

Interventions
The therapies being considered are myeloablative or reduced intensity conditioning allogeneic hematopoietic cell transplant.

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

Review of Evidence

Myeloablative Conditioning Allogeneic Hematopoietic Cell Transplantation
Despite the successes seen with drugs now available to treat myelodysplastic syndromes (MDS; e.g., decitabine, azacitidine, lenalidomide), allogeneic hematopoietic cell transplantation (allo-HCT) is the only treatment capable of complete and permanent eradication of the MDS clone.(7)

Systematic Reviews
A 2009 review of HCT for MDS evaluated the evidence for allo-HCT with myeloablative conditioning (MAC) for MDS.(8) Reviewers selected 24 studies (prospective and retrospective) published between 2000 and 2008 that included a total 1378 cases (age range, 32-59 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 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 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 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 Allogeneic Hematopoietic Cell Transplantation

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). Non-relapse mortality was significantly improved with RIC as compared to total body irradiation/busulfan-based MAC (HR, 0.53; 95% CI, 0.36 to0.8; p=.002); however, treosulfan-based MAC significantly reduced non-relapse mortality as compared to RIC (HR, 1.67; 95% CI, 1.02to 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 myeloablative regimens before allo-HCT in patients with MDS.(12,13,14) 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 1 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 reduced-intensity and myeloablative conditioning 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 reduced-intensity conditioning (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 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.(32) 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 [OR] 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).(33) 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), but they had significantly higher 3-year incidence of relapse than patients treated with MAC (29.9% vs 22.8%; p=0.029).

Kim et al (2012) published a phase 3 randomized trial (n = 83 patients) comparing the toxicity rates for 2 different conditioning regimens (reduced CY, fludarabine, and antithymocyte globulin [ATG]; standard Cy-ATG).(34) Four patients had MDS, and the remaining study patients had severe aplastic anemia. Overall, the incidence of 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.

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)	52 pediatric patients with MDS	• Allo-HCT (59% with related donors) • Stem cell source: o Bone marrow, 63% o Peripheral blood, 26% o Umbilical cord blood, 11%	• 5-y DFS=50% • 5-y OS=55%
Boehm et al (2014)	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)	128 adults with MDS: 40 received AZA before HCT and 88 received BSC	RIC allo-HCT	• 3-y OS=53% in AZA group vs. 53% in BSC group (p=0.69) • 3-y RFS=37% in AZA group vs. 42% in BSC group (p=0.78) • 3-y NRM=20% in AZA group vs. 23% in BSC group (p=0.74)
Di Stasi et al (2014)	227 patients with MDS or AML	• Allo-HCT • Donor source:	3-y PFS for patients in remission:

		o Matched-related, 38% o Matched-unrelated, 48% o Haploidentical, 14%	• 57% for matched-related • 45% for matched-unrelated • 41% for haploidentical (p=0.417)
Onida et al (2014)	• 523 patients with MDS • IPSS cytogenic risk group: o Good risk: 53.5% o Intermediate risk: 24.5% o Poor risk: 22%	• Allo-HCT • RIC in 12%	5-y OS based on IPSS cytogenic risk group: • Good: 48% • Intermediate: 45% • Poor: 30%
Oran et al (2014)	• 256 patients with MDS • Pretreatment: o No cytoreductive chemo: 30.5% o Chemo: 15.6% o HMA: 47.7% o Chemo + HMA: 6.2%	• Allo-HCT • RIC in 36.7%	3-y EFS based on cytoreductive therapy: • No cytoreductive chemo: 44.2% • Chemo: 30.6% • HMA: 34.2% • Chemo + HMA: 32.8% (p=0.50)
Yoshimi et al (2014)	17 children with secondary MDS or AML after childhood aplastic anemia	• Allo-HCT	5-y OS and EFS=41%
Basquiera et al (2016)	• 84 adults with MDS Cytogenic risk group: o Standard: 65.5% o Adverse: 12.6% o 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)	• 513 adults with CMML • Pretreatment: o No prior disease-modifying therapy: 28% o Disease-modifying therapy: 72%	• Allo-HCT • RIC in 41.6%	• 1-y NRM=31% • 4-y NRM=41% • 4-y RFS=27% • 4-y OS=33%
Pohlen et al (2016)	• 187 patients with refractory AML (87%) or high-risk MDS (13%)	• Allo-HCT • RIC in 52% • Unrelated donors in 73% • Stem cell source: o Bone marrow, 6% o 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)	• 313 adults with MDS and secondary AML, age ≥ 70 Cytogenic risk group: o Good: 51% o Intermediate: 22% o Poor/very poor: 11%	• Allo-HCT • RIC or non-MAC in 83% • Unrelated donors in 75% • Stem cell source: o Bone marrow, 6% o Peripheral blood, 94%	• 1-y NRM: 32% • 3-y relapse: 28% • 3-y OS: 34%

Robin et al (2022)	• 1114 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<.001)
			  ○ Higher-risk disease: 27% with allo-HCT vs. 15% without allo-HCT (p=.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 intensity 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; CI: confidence interval; CMML: chronic myelomonocytic leukemia; DFS: disease-free survival; EFS: event-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; PFS: progression-free survival; RFS: relapse-free survival; RIC: reduced-intensity conditioning.

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. 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 myeloablative conditioning HCT.

MYELOPROLIFERATIVE NEOPLASMS

Clinical Context and Therapy Purpose

The purpose of myeloablative conditioning and reduced-intensity conditioning allogeneic hematopoietic cell transplant in individuals who have myeloproliferative neoplasms is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICOs were used to select literature to inform this review.

Populations
The relevant population of interest are patients who have myeloproliferative neoplasms.

Interventions
The therapies being considered are myeloablative conditioning or reduced-intensity conditioning allogeneic hematopoietic cell transplant.

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

Outcomes
The general outcomes of interest are mortality and morbidity. Follow-up over months to years is of interest for relevant outcomes. Beneficial outcomes are an improvement in overall survival and disease-specific survival. 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.

Review of Evidence
Data on therapy for myeloproliferative neoplasms (MPN) are sparse.(29,48,49) As outlined in this evidence review, with the exception of MAC chemotherapy and allo-HCT, no therapy has yet been proven to be curative or to prolong survival of individuals 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%), and55% (95% CI, 51.8% to 58.3%), respectively. Non-relapse mortality rates for the same time periods were 25.9% (95% CI, 23.3% to28.7%), 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 of 289 patients treated between 1989 and 2002, from the database of the Center for International Bone Marrow Transplant Research.(51) 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. 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 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.(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 four European transplant centers between 1998 and 2005. Twenty-three patients (median age, 47 years; range, 31-60 years) underwent myeloablative conditioning and 23 patients (median age, 54 years; range, 38-74 years) underwent RIC. The majority in both groups (85%) were deemed intermediate or high risk. At a median follow-up of 50 months (range, 20-89 months), there was a trend for a better progression-free survival rate at 3 years in RIC patients than in myeloablative conditioning 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). Non-relapse mortality rates at 3 years trended higher in myeloablative conditioning 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.

Section Summary: Myeloproliferative Neoplasms
Observational studies of HCT for myeloproliferative neoplasms 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 individuals 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 individuals 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 syndrome (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 (PFS) 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 myeloproliferative neoplasms who receive MAC or RIC allo-HCT, the evidence includes a systematic review and 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 has suggested that RIC may be used in individuals who are older and have more comorbidities without significantly worsening overall survival. 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 individuals with myeloproliferative neoplasms. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network Guidelines
Current National Comprehensive Cancer Network (NCCN) clinical practice guidelines for myelodysplastic syndromes (MDS) 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 MDS are outlined in Table 2.(53)

Table 2. Guidelines for Allo-HCT 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 erythropoetin 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
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 on the use of allo-HCT for the treatment of myeloproliferative neoplasms (MPN).(53) The guideline notes 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

Prognostic Category	Recommendations for Allo-HCT
Lower risk myelofibrosis MIPSS-70 ≤ 3 MIPSS-70+ Version 2.0 ≤ 3 DIPSS-Plus ≤ 1 DIPPS ≤ 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 MIPSS-70 ≥ 4 MIPSS-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 patients 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; MIPSS: Mutation-Enhanced International Prognostic Scoring System. MYSEC-PM: Myelofibrosis Secondary to PV [polycythemia vera] and ET [essential thrombocythemia]-Prognostic Model; JAK: Janus kinase.

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 in adults.

Table 4. Recommendations for the Use of HCT to Treat Myelodysplastic Syndromes, Myelofibrosis, and Myeloproliferative Neoplasms

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")

In 2023, the ASTCT published practice recommendations for HCT in the management of myelodysplastic syndromes. A standardized system for grading the levels of evidence was applied (as recommended by the ASTCT Steering Committee for evidence-based reviews). Table 5 summarizes allo-HCT specific recommendations by ASTCT.

Table 5. Recommendations for the Use of Allogeneic Hematopoietic Cell Transplantation to Treat Myelodysplastic Syndromes

Indication/ Consideration	Recommendation	Grade of Recommendation
Should allogeneic HCT routinely be offered early for advanced (int-2/high) de novo MDS?	Yes	A
Should allogeneic HCT routinely be offered early for lower risk (low/int-1) de novo MDS?	No	B

HCT: hematopoietic cell transplantation; MDS: myelodysplastic syndrome.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 6.

Table 6. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
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.

Government Regulations
National:

There are numerous autoimmune diseases and the Centers for Medicare and Medicaid Services have not issued a national coverage determination (NCD) for stem cell transplantation for each disease. CMS has a general NCD for stem cell transplantation.

Medicare National Coverage Determinations Manual 100-3, Chapter 1, Part 2, Section 110.23, "Stem Cell Transplantation." Effective date: 1/27/16; Implementation Date: 10/3/16

A. General

Allogeneic hematopoietic stem cell transplantation (HSCT) is a procedure in which a portion of a healthy donor's stem cell or bone marrow is obtained and prepared for intravenous infusion. Allogeneic HSCT may be used to restore function in recipients having an inherited or acquired deficiency or defect. Hematopoietic stem cells are multi-potent stem cells that give rise to all the blood cell types; these stem cells form blood and immune cells. A hematopoietic stem cell is a cell isolated from blood or bone marrow that can renew itself, differentiate to a variety of specialized cells, can mobilize out of the bone marrow into circulating blood, and can undergo programmed cell death, called apoptosis - a process by which cells that are unneeded or detrimental will self-destruct.

The Centers for Medicare & Medicaid Services (CMS) is clarifying that bone marrow and peripheral blood stem cell transplantation is a process which includes mobilization, harvesting, and transplant of bone marrow or peripheral blood stem cells and the administration of high dose chemotherapy or radiotherapy prior to the actual transplant. When bone marrow or peripheral blood stem cell transplantation is covered, all necessary steps are included in coverage. When bone marrow or peripheral blood stem cell transplantation is non-covered, none of the steps are covered.

Indications and Limitations of Coverage

B. Nationally Covered Indications

I. Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

a) Effective for services performed on or after August 1, 1978, for the treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary,

b) Effective for services performed on or after June 3, 1985, for the treatment of severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome.

c) Effective for services performed on or after August 4, 2010, for the treatment of Myelodysplastic Syndromes (MDS) pursuant to Coverage with Evidence Development (CED) in the context of a Medicare-approved, prospective clinical study.

MDS refers to a group of diverse blood disorders in which the bone marrow does not produce enough healthy, functioning blood cells. These disorders are varied with regard to clinical characteristics, cytologic and pathologic features, and cytogenetics. The abnormal production of blood cells in the bone marrow leads to low blood cell counts, referred to as cytopenias, which are a hallmark feature of MDS along with a dysplastic and hypercellular-appearing bone marrow

Medicare payment for these beneficiaries will be restricted to patients enrolled in an approved clinical study. (see Determination for further information regarding study criteria)

d) Effective for claims with dates of service on or after 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.

All CMS-approved clinical studies and registries must adhere to the below listed standards of scientific integrity and relevance to the Medicare population as listed in section g. (see full determination for more information).

e) Effective for claims with dates of service on or after 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.

(This NCD last reviewed January 2016.)

National Coverage Analysis - Decision Memo: Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for Myelodysplastic Syndromes (MDS) Published: March 6, 2024.

Final Decision: We are expanding Medicare coverage for allogeneic hematopoietic stem cell transplant using bone marrow, peripheral blood or umbilical cord blood stem cell products for Medicare patients with myelodysplastic syndromes who have prognostic risk scores of:

- ≥ 1.5 (Intermediate-2 or high) using the International Prognostic Scoring System (IPSS), or
- ≥ 4.5 (high or very high) using the International Prognostic Scoring System - Revised (IPSS-R), or
- ≥ 0.5 (high or very high) using the Molecular International Prognostic Scoring System (IPSS-M).

Local:

There is no local coverage determination on this topic. Refer to NCD.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- BMT – Allogenic Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias
- BMT – Autologous, for Malignant Astrocytomas and Gliomas
- BMT – Hematopoietic Cell Transplant for Chronic Lymphocytic Leukemia
- BMT – Hematopoietic Cell Transplant for Treatment of Multiple Myeloma
- BMT – Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia
- BMT – Hematopoietic Cell Transplantation for Acute Myeloid Leukemia
- BMT – Hematopoietic Cell Transplantation for Autoimmune Diseases
- BMT – Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma - Autologous or Allogeneic
- BMT – Hematopoietic Cell Transplantation for CNS Embryonal Tumors and Ependymoma
- BMT – Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer
- BMT – Hematopoietic Cell Transplantation for Hodgkin Lymphoma
- BMT – Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
- BMT – Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
- BMT – Hematopoietic Cell Transplantation for Primary Amyloidosis
- BMT – Hematopoietic Cell Transplantation for Solid Tumors of Childhood
- BMT – Hematopoietic Cell Transplantation for Waldenström's Macroglobulinemia
- BMT – Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors
- Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant
- Orthopedic Applications of Stem-Cell Therapy (Including Allografts and Bone Substitutes used with Autologous Bone Marrow)

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 3/12/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/13	6/18/13	6/26/13	Joint policy established
9/1/14	6/20/14	6/23/14	Added the following codes to the policy: 38220, 38221, 38242, 38243, 81265, 81266, 81267, 81268, 81370, 81371, 81372, 81373, 81374, 81375, 81376, 81377, 81378, 81379, 81380, 81381, 81382, 81383, S2140, S2142, S2150
9/1/15	6/19/15	7/16/15	Updated rationale and references. No substantive changes to policy. Policy status unchanged.
9/1/16	6/21/16	6/21/16	Routine maintenance – rationale and references updated
9/1/17	6/20/17	6/20/17	Routine maintenance References, rationale, Medicare information, and WHO classifications updated Added procedure code 38207
9/1/18	6/19/18	6/19/18	Routine maintenance Removed procedure codes 38220 and 38221
9/1/19	6/18/19		Routine maintenance
9/1/20	6/16/20		• Routine maintenance • RIC inclusions clarified to include age as well as comorbidities
9/1/21	6/15/21		• Routine maintenance
9/1/22	6/21/22		• Routine maintenance
9/1/23	6/13/23		• Routine maintenance (slp) • Vendor Managed: N/A • Criteria clarified via SME input (Regimen removed from inclusion bullet)
9/1/24	6/11/24		• Routine maintenance (slp) • Vendor Managed: N/A

			• Decision memo added – Medicare covers BMT for MDS with criteria

Next Review Date: 2nd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: BONE MARROW TRANSPLANT-HEMATOPOIETIC CELL TRANSPLANTATION FOR MYELODYSPLASTIC SYNDROMES AND MYELOPROLIFERATIVE NEOPLASMS, ALLOGENEIC

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply. Transportation, meals and lodging expenses related to the transplant are not covered unless specifically noted in the member's certificate/rider.
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.