Regence

Medical Policy Manual Transplant, Policy No. 45.24

Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

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Next Review: August 2025
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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

I. Allogeneic hematopoietic cell transplantation (using either reduced-intensity conditioning or myeloablative conditioning) may be considered **medically necessary** to treat either of the following (A. or B.):

   A. Myelodysplastic syndromes; or

   B. Myeloproliferative neoplasms.

II. Subsequent allogeneic hematopoietic cell transplantation using myeloablative conditioning after a previous allogeneic hematopoietic cell transplant with reduced intensity conditioning is considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

ALLOGENEIC HCT

Allogeneic HCT may be considered for patients as follows:

Table 1 summarizes the NCCN recommendations for allogeneic HCT to treat Myelodysplastic Syndromes [v.1.2024]):[1]

Table 1: NCCN Guidelines for Allogeneic HCT for Myelodysplastic Syndromes

Prognostic Category	Recommendations for HCT
IPSS low/intermediate-1 OR IPSS-R very-low, low, intermediate OR WPSS very low, low, intermediate OR	Consider allogeneic HCT for patients who have clinically relevant thrombocytopenia or neutropenia with disease progression or no response after azacitidine/decitabine or immunosuppressive therapy, and no mutant m*IDH1.* Consider allogeneic HCT for patients who have symptomatic anemia with no 5q deletion, with serum erythropoietin level >500 mU/mL, with poor probability of response to immunosuppressive therapy, and no response or intolerance to azacitidine/decitabine or immunosuppressive therapy, and no m*IDH1*.
IPSS intermediate-2, high OR IPSS-R intermediate, high, very high OR WPSS high, very high	Recommend allogeneic 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; NCCN: National Comprehensive Cancer Network; WPSS: WHO Classification-based Prognostic Scoring System.

Table 2 summarizes the NCCN recommendations for the use of allogeneic HCT for the treatment of myeloproliferative neoplasms (MPN; v.1.2024).[2]

Table 2: NCCN Guidelines for Allogeneic HCT for Myeloproliferative Neoplasms

Prognostic Category	Recommendations for Allogeneic HCT
Lower-risk myelofibrosis	Evaluation for allogeneic HCT is recommended for patients with low platelet counts or complex cytogenetics.
Higher-risk myelofibrosis	Evaluation for allogeneic HCT is recommended for all patients. For transplant candidates, allogeneic transplant is recommended. Selection of allogeneic HCT should be based on age, performance status, major comorbid conditions, psychosocial status, patient

Prognostic Category	Recommendations for Allogeneic HCT
	preference, and availability of caregiver. Patients may be taken immediately to transplant or bridging therapy can be used to decrease marrow blasts to an acceptable level prior to transplant.
Disease progression to advanced stage/AML	Clinical trial or induce remission with hypomethylating agents or intensive induction chemotherapy followed by allogeneic HCT. The guideline notes that selection of allogeneic HCT should be based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver. Patients may be taken immediately to transplant or bridging therapy can be used to decrease marrow blasts to an acceptable level prior to transplant.

allo: allogeneic; AML: acute myeloid leukemia; DIPSS: Dynamic International Prognostic Scoring System; HCT: hematopoietic cell transplantation; IPSS: International Prognostic Scoring System; NCCN: National Comprehensive Cancer Network.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
2. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16
3. Hematopoietic Cell Transplantation for Acute Myeloid Leukemia, Transplant, Policy No. 45.28
4. Hematopoietic Cell Transplantation for Chronic Myelogenous Leukemia, Transplant, Policy No. 45.31

BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION

Broadly speaking, there are two types of hematopoietic cell transplants (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease (e.g. lymphoma) with myeloablative doses of chemotherapy (with or without radiation) that are active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA A, B, and DR loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

CONVENTIONAL PREPARATIVE CONDITIONING FOR HCT

The conventional ("classical") practice of allogeneic HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that develops after engraftment of allogeneic cells within the patient's bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HCT

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden, but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells.

For the purposes of this Policy, the term "reduced-intensity conditioning" will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

MYELODYSPLASTIC SYNDROMES

Myelodysplastic syndromes or neoplasms (MDS) refer to a heterogeneous group of clonal hematopoietic disorders characterized by impaired maturation of hematopoietic cells and a tendency to transform into acute myelocytic leukemia (AML). MDS can occur as a primary (idiopathic) disease, or be secondary to cytotoxic therapy, ionizing radiation, or other environmental insult. Chromosomal abnormalities are seen in 40%–60% of patients, frequently

involving deletions of chromosome 5 or 7, or an extra chromosome as in trisomy 8. The vast majority of MDS diagnoses occur in individuals over the age of 55–60 years, with an age-adjusted incidence of about 62% among individuals over age 70 years. Patients either succumb to disease progression to AML or to complications of pancytopenias. Patients with higher blast counts or complex cytogenetic abnormalities have a greater likelihood of progressing to AML than do other patients.

Risk Stratification of MDS

Risk stratification for MDS is performed using the IPSS (see Table PG1). This system was developed after pooling data from seven studies that used independent, risk-based prognostic factors. The prognostic model and the scoring system were built based on blast count, degree of cytopenia, and blast percentage. Risk scores were weighted relative to their statistical power. This system is widely used to divide patients into two categories: (1) low-risk and (2) high-risk groups (see Table PG2). The low-risk group includes low-risk and Int-1 IPSS groups; the goals in low-risk MDS patients are to improve quality of life and achieve transfusion independence. In the high-risk group—which includes intermediate-2 and high-risk IPSS groups—the goals are slowing the progression of disease 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 becomes worse 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	–	–	–

Table PG2. International Prognostic Scoring System: Myelodysplastic Syndrome Clinical Outcomes

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

AML: acute myelocytic leukemia.

Since 1997, the International Prognostic Scoring System (IPSS) has been used to assess prognosis of primary untreated adult MDS patients. The IPSS were refined in 2012 by Greenberg and is referred to as the IPSS-R. Five prognostic subgroups were specified, expanding on the IPSS four group classification. Patient age, performance status, serum ferritin, and lactate dehydrogenase were included in the development of this system for survival but not for acute myeloid leukemia transformation.[3] The cytogenetic classification of the IPSS-R has since been found to have added value in predicting patient outcomes as compared to prediction models using only the traditional risk factors or the three-group IPSS cytogenetic classification.[4]

The WHO subgroup classification adds morphologic refinement of the French-American-British (FAB) classification. The WHO Prognostic Scoring System (WPSS) accounts for blast percentage, cytogenetics, and severity of cytopenias as assessed by transfusion requirements.

MDS Treatment

Treatment of smoldering or nonprogressing MDS has in the past involved best supportive care including red blood cell (RBC) and platelet transfusions and antibiotics. Active therapy was given only when MDS progressed to AML or resembled AML with severe cytopenias. A diverse array of therapies are now available to treat MDS, including hematopoietic growth factors (e.g., erythropoietin, darbepoetin, granulocyte colony-stimulating factor), transcriptional-modifying therapy (e.g., U.S. Food and Drug Administration [FDA]-approved hypomethylating agents, non-approved histone deacetylase inhibitors), immunomodulators (e.g., lenalidomide, thalidomide, antithymocyte globulin, cyclosporine A), low-dose chemotherapy (e.g., cytarabine), and allogeneic HCT. Given the spectrum of treatments available, the goal of therapy must be decided upfront, whether it is to improve anemia, thrombocytopenia, or neutropenia; eliminate the need for RBC transfusion; achieve complete remission (CR); or, cure the disease. Allogeneic HCT is the only approach with curative potential, but its use is governed by patient age, performance status, medical comorbidities, the patient's risk preference, and severity of MDS at presentation.

MYELOPROLIFERATIVE NEOPLASMS

The MPNs are clonal bone marrow stem-cell disorders characterized by the slow but relentless expansion of a clone of cells with the potential evolution into a blast crisis similar to AML. They share a common stem cell-derived clonal heritage, with phenotypic diversity attributed to abnormal variations in signal transduction as the result of a spectrum of mutations that affect protein tyrosine kinases or related molecules. The unifying characteristic common to all MPNs is effective clonal myeloproliferation resulting in peripheral granulocytosis, thrombocytosis, or erythrocytosis that is devoid of dyserythropoiesis, granulocytic dysplasia, or monocytosis.

As a group, about 8,400 MPNs are diagnosed annually in the U.S. Like MDS, MPNs occur primarily in older individuals, with about 67% reported in patients aged 60 years and older. In indolent, nonprogressing cases, therapeutic approaches are based on relief of symptoms. Myeloablative allogeneic HCT has been considered the only potentially curative therapy, but because most patients are of advanced age with attendant comorbidities, its use is limited to those who can tolerate the often severe treatment-related adverse effects of this procedure. However, the use RIC of conditioning regimens for allogeneic HCT has extended the potential benefits of this procedure to selected individuals with these disorders.

MPN Classification and Risk Stratification

In 2008, a new WHO classification scheme replaced the term chronic myeloproliferative disorder (CMPD or MPD) with the term myeloproliferative neoplasms (MPN). The 2016 classification update is not a significant change in disease categories, but rather, an incorporation of the new knowledge of the diseases accumulated since 2008.[5] The myeloproliferative neoplasms include:

- Chronic myeloid leukemia (CML)
- Chronic neutrophilic leukemia (CNL)
- Polycythemia vera (PV)
- Primary myelofibrosis (PMF)
- Essential thrombocytopenia (ET)
- Chronic eosinophilic leukemia, not otherwise specified (NOS)
- MPN, unclassifiable
- Mastocytosis

See Appendix I for the full WHO myeloid neoplasm and acute leukemia classification.

Amongst each of the MPNs, risk stratification is based on clinical findings at diagnosis. For primary myelofibrosis, post-PV, or post-ET MF, the International Prognostic Scoring System (IPSS), Dynamic International Prognostic Scoring System (DIPSS), or DIPSS-PLUS may be used. Other factors such as age and history of thrombosis factor in to other MPN risk stratification.

MPN Treatment

In indolent, nonprogressing cases, therapeutic approaches are based on relief of symptoms. Supportive therapy may include prevention of thromboembolic events. Hydroxyurea may be used in cases of high-risk essential thrombocytosis and polycythemia vera and intermediate- and high-risk primary myelofibrosis.

In November 2011, the FDA approved the orally-administered selective Janus kinase 1 and 2 inhibitor ruxolitinib for the treatment of intermediate- or high-risk myelofibrosis. Ruxolitinib has been associated with improved OS, spleen size, and symptoms of myelofibrosis when compared with placebo.[6]

NOTES:

- Chronic myeloid leukemia and acute myeloid leukemia are considered in separate medical policies (see Cross References).
- For additional information regarding MDS and MPN classification see the WHO strata listed in Appendix I.

EVIDENCE SUMMARY

The principal outcomes associated with treatment of hematologic malignancies are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Risk of graft-versus-host disease is another primary outcome among patients undergoing allogeneic hematopoietic cell transplantation (HCT). Ideally, in order to understand the impact of HST for treatment of myelodysplastic syndromes and myeloproliferative neoplasms, clinical trials that compare HCT using either a myeloablative or reduced intensity conditioning regimen to standard medical treatments are needed. Further, for treatment of malignancies, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits associated with treatment to understand the net treatment effect.

MYELODYSPLASTIC SYNDROMES (MDS)

Despite the successes seen with new drugs now available to treat MDS (e.g., decitabine, azacitidine, lenalidomide), allogeneic HCT is the only treatment capable of complete and permanent eradication of the MDS clone.[7] The recommendations of a systematic review of the role of allogeneic HCT in patients with MDS prepared by the American Society for Blood and Marrow Transplantation (ASBMT) are congruent with the present policy statements.[8] Other reviews concur with the ASBMT recommendations.[9-11] For example, a review of allogeneic HCT using myeloablative conditioning for MDS included 24 studies (prospective and

retrospective) published between 2000 and 2008 that included a total 1,378 cases with age range of 32 to 59 years.[12] A majority of patients (n=885) received matched related donor (MRD) allogeneic HCT, with other donor types including syngeneic, matched, unrelated donor (MUD), mismatched unrelated donor (URD), and umbilical cord blood. Most studies included de novo and secondary MDS, chronic myelomonocytic leukemia, and myeloproliferative neoplasms (MPNs), de novo and secondary acute myelocytic 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 (BU/CY) and CY plus total body irradiation (CY/TBI), with cyclosporine A (CYA) used for graft-versus-host disease (GVHD) prophylaxis. Length of follow-up ranged from five months to about eight years. Grades II-IV acute GVHD varied from 18% to 100%. Relapse risk ranged from a low of 24% at one year to 36% at five years. Overall survival (OS) ranged from 25% at two years to 52% at four years, with non-relapse mortality (NRM) ranging from 19% at day 100 to 61% at five years.

Smaller studies continue to report outcomes from HCT for MDS in variety of patient populations and to evaluate the impact of specific patient and donor characteristics on outcomes.[13-21] In addition, studies reporting on outcomes specific to conditioning regimens are available.[22-25]

Recent studies have compared RIC and myeloablative conditioning (MAC) regimens before allogeneic HCT in patients with MDS.[26-28] A systematic review (SR) with meta-analysis by Song (2021) evaluated the efficacy and safety of RIC vs. MAC for AML in complete remission and MDS across six randomized controlled trials (RCTs) with 1,413 participants (711 in RIC, 702 in MAC).[29] Across trials, RIC had the same OS (HR=0.95, 95% CI 0.64 to 1.4, p=0.80) and cumulative incidence of relapse as MAC (HR=1.18, 95% CI 0.88 to 1.59, p=0.28). Non-relapse mortality was significantly reduced in the RIC group compared to the total body irradiation/busulfan-based MAC group (HR=0.53, 95% CI 0.36 to 0.80, p=0.002). The RIC group had similar graft failure as MAC. The authors conclude that RIC conditioning can be recommended for preparative treatment before allogeneic HCT for patients with AML in complete remission or MDS.

Ma (2020) published a SR of RIC compared to MAC in younger adults (younger than 66 years) with myelodysplastic syndrome and AML.[30] The review and meta-analysis evaluated four RCTs (n=633), including the studies by Scott and Kroger summarized below. The overall risk of bias of the included RCTs was moderate. No significant difference in PFS or relapse incidence (RI) were found at one, two, four, or five years between the two conditioning intensities. OS was similar at one, two and four years, but patients receiving RIC had a higher OS at five years. RIC was associated with lower non-relapse mortality, less grade II-IV and grade III-IV acute graft-versus-host disease (GVHD), and lower incidence of chronic GVHD compared with MAC regimens. The authors concluded that RIC is a feasible treatment option for adults younger than 65 with AML or MDS, particularly those with intermediate-risk disease. Additional research is needed to inform treatment decisions specific to patient characteristics.

RCTs are heterogenous in patient characteristics and conditioning regimens and their findings are varied based on these differences. In patients who were considered eligible for standard MAC (e.g., median age 50-55; HCT Comorbidity Index less than 4), results were mixed between studies that compared RIC to standard MAC regimens. In the European Society of Blood and Marrow Transplantation RCT by Kroger (2017), of 129 patients from 18 centers

primarily with MDS (median age=50 years; HCT Comorbidity Index NR), RIC and MAC had similar rates of two-year relapse (17% versus 15%; p=0.6), relapse-free survival 62% versus 58%; p=0.58) and overall survival (76% versus 63%, p=0.08).[27] In contrast, in a RCT by Scott (2017), enrollment was stopped early in 272 patients (median age=55 years; 67% had HCT Comorbidity Index of 0-3; 80% AML) because of a significantly greater risk of relapse at 18 months with RIC (48.3% versus 13.5%; p<0.001).[28] At that time, overall survival was similar for MAC versus RIC (77.5% versus 67.7%; difference=9.8%; 95% CI, -0.8 to 20.3%). These findings suggest use of RIC allo-HCT may put MAC-eligible patients at a disadvantage in some circumstances. Long-term outcomes (median 51 months, range 5 to 80 months) of the RCT by Scott were published in 2021.[31] The study cohort included 54 patients with MDS and 218 patients with AML. At four years post-treatment, the transplant-related mortality (TRM) was significantly higher for MAC at 25.1%, compared with 9.9% for RIC (p<0.001). Patients who received RIC had a significantly higher risk of relapse compared to those who received MAC (hazard ratio [HR], 4.06; 95% CI, 2.59 to 6.35; p<0.001). No significant difference in post-relapse survival at three years was found between groups (24% for MAC and 26% for RIC). OS was higher for MAC compared to RIC (HR, 1.54; 95% CI, 1.07 to 2.2; p=0.03). Importantly, these findings were driven primarily by data from the AML subset; the small sample of MDS patients precludes evaluation of the outcomes specific to MDS.

In a RCT by Beelan (2019), patients who were considered ineligible for standard MAC based on age (greater than or equal to 50 years), an HCT comorbidity index of more than two, or both, a reduced toxicity MAC regimen (treosulfan plus fludarabine) was compared to RIC.[26] Findings in the overall population (n=476; 64% acute myeloid leukemia; 36% MDS) suggest a superior two-year event-free survival with the reduced-toxicity MAC regimen (HR O.65; 95% CI, 0.47 to 0.90; p<0.001 for noninferiority and p<0.0051 for superiority) and a similar relapse or progression (HR 0.87; 95% CI, 0.59 to 1.30). However, in the MDS subgroup (n=167), differences between the reduced-toxicity MAC regimen and the RIC regimen were not statistically significant for event-free survival (HR 0.70; 95% CI, 0.36 to 1.36) or relapse or progression (HR 0.92; 95% CI, 0.58 to 1.48). The incidence of two-year overall survival in both groups (approximately 48% to 68%) appear numerically greater than those described above from an earlier 2009 review of MAC for MDS (25%), suggesting that RIC or reduced toxicity MAC may be a reasonable strategy for those who may be MAC-intolerant.[12] These findings also appear consistent with the American Society for Blood and Marrow Transplantation's (2009) SR (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."[8] Other reviews (2010-2012) have also drawn conclusions similar to those of the American Society for Blood and Marrow Transplantation.[9-11, 32, 33] Given the absence of curative therapies for these patients, RIC allo-HCT may be considered as a treatment strategy for patients with MDS who could benefit from allo-HCT but who are at high-risk of MAC regimen intolerance.

Additional evidence from uncontrolled studies on RIC with allogeneic HCT shows long-term remissions (i.e., longer than four years) can be achieved, often with reduced treatment-related morbidity and mortality, in patients with MDS/AML who otherwise would not be candidates for myeloablative conditioning regimens.[12, 28, 34-48] These prospective and retrospective studies included cohorts of 16 to 215 patients similar to those in the myeloablative allogeneic 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–IV GVHD was 9-63%, with relapse risk of 6 to 61%. The OS rates ranged between 44% at one year to 46% at five years, with a median follow-up range of 14 months to over four years.

MYELOPROLIFERATIVE NEOPLASMS

Data on therapy for myeloproliferative neoplasms (MPN) remain sparse.[41, 43, 49] As outlined previously in this policy, with the exception of myeloablative chemotherapy and allogeneic HCT, no therapy has yet been proven to be curative or to prolong survival of patients with MPN. The significant toxicity of myeloablative conditioning and allogeneic HCT in MPN has led to study of the use of RIC regimens for these diseases.

Bewersdorf (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 mainly retrospective studies. 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 one-, two-, and five-year survival. Rates of non-relapse mortality, RFS or progression-free survival (PFS), and safety were also evaluated. Regarding survival, one-year, two-year, and five-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 one-, two- and five-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.

Kroger compared outcomes for patients treated with allo-HCT (n=190) or conventional therapies (n=248) at diagnosis in patients with primary myelofibrosis who were under 65 years old at diagnosis.[51] In the HCT group, 91 and 97 subjects received RIC and MA conditioning, respectively. Patients at low risk based on the Dynamic International Prognostic Scoring System model treated with HCT had a relative risk of death, compared with conventionally treated patients, of 5.6 (95% CI, 1.7 to 19; p=0.005). In contrast, those with intermediate-2 and high risk treated with HCT had a relative risk of death, compared with conventionally treated patients, of 0.55 (95% CI, 0.36 to 0.83; p=0.005) and 0.37 (95% CI, 0.21 to 0.66; p<0.001), respectively. Intermediate-1 patients treated with HCT did not significantly differ in risk of death from those treated with conventional therapies. Although the study design was limited by the potential for bias due to patient selection, these results support using prognosis to guide decisions about HCT for primary myelofibrosis.

The largest study of allogeneic HCT for primary myelofibrosis comes from retrospective analysis by Ballen (2010) of the outcomes of 289 patients treated between 1989 and 2002, from the database of the Center for International Bone Marrow Transplant Research (CIBMTR).[52] The median age was 47 years (range: 18 to 73 years). Donors were HLA-identical siblings in 162 patients, unrelated individuals in 101 patients, and HLA non-identical family members in 26 patients. Patients were treated with a variety of conditioning regimens

and GVHD prophylaxis regimens. Splenectomy was performed in 65 patients prior to transplantation. The 100-day treatment-related mortality was 18% for HLA identical sibling transplants, 35% for unrelated transplants, and 19% for transplants from alternative related donors. Corresponding five-year OS rates were 37%, 30%, and 40%, respectively. DFS rates were 33%, 27%, and 22%, respectively. DFS for patients receiving reduced-intensity transplants was comparable: 39% for HLA identical sibling donors and 17% for unrelated donors at three years. In this large retrospective series, allogeneic transplantation for myelofibrosis resulted in long-term relapse-free survival (RFS) in about one-third of patients.

One case series of 148 patients included 27 (mean age: 59 years) with MPN who underwent allogeneic HCT using a RIC regimen of low-dose (2 Gy) total body irradiation alone or with the addition of fludarabine.[44] At a median follow-up of 47 months, the three-year relapse-free survival was 37% and overall survival was 43%, with a three-year nonrelapse mortality of 32%.

In a second series, 103 patients (median age 55 years, range 32 to 68 years) with intermediate to high risk (86% of total patients) primary myelofibrosis (PMF) or post-essential thrombocythemia (PT) and polycythemia vera myelofibrosis (PVM) were included on a prospective multicenter Phase II trial to determine efficacy of a busulfan plus fludarabine-based RIC regimen followed by allogeneic HCT from related (n=33) or unrelated (n=70) donors.[53] Acute grade II-IV GVHD occurred in 27%, and chronic GVHD in 43% of patients. The cumulative incidence of NRM at one year in all patients was 16% (95% confidence interval [CI], 9 to 23%) but reached 38% (95% CI, 15-61%) among those with a mismatched donor versus 12% (95% CI, 5 to 19%) among cases with a matched donor (p=0.003). The cumulative relapse rate at three and five years was 22% (95% CI, 13 to 31%) and 29% (95% CI, 16 to 42%), respectively. After a median follow-up of 33 months (range, 12 to 76 months) five-year estimated disease-free survival (DFS) and OS was 51% (95% CI, 38 to 64%) and 67% (95% CI, 55 to 79%), respectively.

A retrospective study in 2009 analyzed the impact of conditioning intensity on outcomes of allogeneic HCT in patients with myelofibrosis (MF).[54] This multicenter trial included 46 consecutive patients treated at three Canadian and four European transplant centers between 1998 and 2005. Twenty-three patients (median age 47 years, range 31 to 60 years) underwent myeloablative conditioning, and 23 patients (median age 54 years, range 38 to74 years) underwent RIC. The majority in both groups (85%) were deemed intermediate- or high-risk. At a median follow-up of 50 (range 20 to 89) months, there was a trend for better progression-free survival (PFS) at three years in RIC patients compared to myeloablative-conditioned patients (58%, range 23 to 62 vs. 43%, range 35 to 76, respectively, p=0.11); there was a similar trend in three-year OS (68%, range 45 to 84 vs. 48%, range 27-66, respectively, p=0.08). Non-relapse mortality rates at three years trended higher in myeloablative conditioned cases than RIC cases (48%, range 31 to 74 vs. 27%, range 14 to 55, respectively, p=0.08). The results of this study suggest that both types of conditioning regimens have curative potential in patients with MF. Despite the RIC patients being significantly older with longer disease duration and poorer performance status than those who received conventional conditioning, the groups had similar outcomes, supporting the use of RIC allogeneic HCT in this population.

In a retrospective study in nine Nordic transplant centers, a total of 92 patients with MF in chronic phase underwent allogeneic HCT.[55] Myeloablative (MA) conditioning was given to 40 patients, and RIC was used in 52 patients. The mean age in the two groups at transplantation was 46±12 and 55±8 years, respectively (p<0.001). When adjustment for age differences was made, the survival of the patients treated with RIC was significantly better (p=0.003). Among

the RIC patients, survival was significantly (p=0.003) greater for patients younger than age 60 years (a 10-year survival close to 80%) than for patients older than 60 years. The stem-cell source did not significantly affect the survival. No significant difference was found in NRM at 100 days between the MA- and the RIC-treated patients. The probability of survival at five years was 49% for the MA-treated patients and 59% in the RIC group (p=0.125). Patients treated with RIC experienced significantly less acute GVHD compared with patients treated with MA conditioning (p<0.001). The OS at five years was 70%, 59% and 41% for patients with Lille score 0, 1 and 2, respectively (p=0.038, when age adjustment was made). Twenty-one percent of the patients in the RIC group were given donor lymphocyte infusion because of incomplete donor chimerism, compared with none of the MA-treated patients (p<0.002). Nine percent of the patients needed a second transplant because of graft failure, progressive disease or transformation to AML, with no significant difference between the groups.

Gupta reported better disease-free survival rates in a more recent analysis of 233 patients with primary myelofibrosis who underwent RIC HCT from 1997 to 2010.[56] Five-year OS was 47% (95% CI, 40% to 53%). Conditioning regimen was not significantly associated with OS.

In a prospective nonrandomized study, Rondelli compared survival outcomes for reduced intensity allogeneic HCT in patients with sibling donors (n=32) or unrelated donors (n=34).[57] Mean follow-up was 25 months for living patients. All outcomes were significantly superior for the patients with sibling donors. Engraftment occurred in 97% of siblings and 76% of unrelated transplants, with overall graft failure rates of 6% and 36%, respectively. Corresponding OS was 75% and 32%, respectively, and nonrelapse mortality was 22% and 59%, respectively. One limitation of this study is that it did not include data on HLA antibodies which may have influence the rejection rate in the unrelated transplant patients. The authors concluded that more data from large prospective studies are needed to determine if donor match can significantly reduce nonrelapse mortality in high risk allogeneic HCT.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK GUIDELINES

Current National Comprehensive Cancer Network (NCCN) clinical practice guidelines for myelodysplastic syndromes (v.1.2024) make the following recommendation about hematopoietic cell transplantation (HCT) in general:[1]

> 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.

Current National Comprehensive Cancer Network (NCCN) clinical practice guidelines for myeloproliferative neoplasms (v.1.2024) make the following recommendation about hematopoietic cell transplantation (HCT):[2]

> For lower-risk myelofibrosis: Evaluation for allogeneic HCT is recommended for patients with low platelet counts or complex cytogenetics. Identification of “higher-risk” mutations may be helpful in the decision-making regarding allogeneic HCT for patients with PMF.

For higher-risk myelofibrosis: Evaluation for allogeneic HCT is recommended for all transplant candidates. Identification of “higher-risk” mutations may be helpful in the decision-making regarding allogeneic HCT for patients with PMF. The selection of patients for allogeneic HCT should be based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver. Patients may be taken immediately to transplant or bridging therapy can be used to decrease marrow blasts to an acceptable level prior to transplant.

SUMMARY

Hematopoietic cell transplantation (HCT) is, at present, the only potentially curative treatment option for patients with myelodysplastic syndromes and myeloproliferative neoplasms. The absence of curative therapies coupled with clinical data and the clinical practice guidelines from the National Comprehensive Cancer Network permit the conclusion that allogeneic HCT using either a myeloablative or reduced-intensity conditioning (RIC) regimen may be considered medically necessary in appropriately selected patients with myelodysplastic syndromes and myeloproliferative neoplasms.

There is not enough research to show that the use of allogeneic hematopoietic cell transplantation (HCT) for the treatment of myelodysplastic syndromes and myeloproliferative neoplasms not meeting policy criteria, including allogeneic myeloablative HCT after a previous reduced intensity conditioning allogeneic HCT, improves health outcomes. Therefore, HCT with or without reduced-intensity conditioning for the treatment of myelodysplastic syndromes and myeloproliferative neoplasms that does not meet the policy criteria is considered investigational.

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CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38207	Transplant preparation of hematopoietic progenitor cells, cryopreservation and storage
	38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38230	Bone marrow harvesting for transplantation; allogeneic
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38242	Allogeneic lymphocyte infusions
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

APPENDIX I

2022 World Health Organization (WHO) Classification of MDS[58]

The myeloid neoplasms are categorized according to criteria developed by the WHO.

WHO myeloid neoplasm and acute leukemia classification

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)

APPENDIX I

- Primary myelofibrosis (PMF)
  - PMF, prefibrotic/early stage
  - PMF, overt fibrotic stage
- 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.

- Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement
- Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement
- Myeloid/lymphoid neoplasms with *FGFR1* rearrangement
- Myeloid/lymphoid neoplasms with *JAK2* rearrangement
- Myeloid/lymphoid neoplasms with *ETV6::ABL1* fusion
- Other defined tyrosine kinase fusions:

ETV6::FGFR2; ETV6::LYN; ETV6::NTRK3; RANBP2::ALK; BCR::RET; FGFR10P::RET

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)

- Chronic myelomonocytic leukemia (CMML)
- Myelodysplastic/myeloproliferative neoplasm with neutrophilia^{-}
- Myelodysplastic/myeloproliferative neoplasm 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-bi*TP53*)
- MDS, morphologically defined
  - MDS with low blasts (MDS-LB)
  - MDS, hypoplastic (MDS-h)

APPENDIX I

MDS with increased blasts (MDS-IB)
MDS-IB1
MDS-IB3
MDS with fibrosis (MDS-f)

Acute myeloid leukemia (AML)

AML with defining genetic abnormalities
Acute promyelocytic leukemia with *PML::RARA* fusion
AML with *RUNX1::RUNX1T1* fusion
AML with *CBFB::MYH11* f*usion*
APL with *DEK::NUP214* fusion
AML with *RBM15::MRTFA* fusion
AML with *BCR::ABL1* fusion
AML with *KMT2A* rearrangement
AML with *MECOM* rearrangement
AML with *NUP98* rearrangement
AML with *NPM1* mutation
AML with *CEBPA* mutation
AML, myelodysplasia-related
AML with other defined genetic alterations
AML, defined by differentiation
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia

Dendritic cell and histiocytic neoplasms

Plasmacytoid dendritic cell neoplasms
Mature plasmacytoid dendritic cell proliferation associated with myeloid neoplasm
Blastic plasmacytoid dendritic cell neoplasm
Langerhans cell and other dendritic cell neoplasms
Langerhans cells neoplasms
Langerhans cell histiocytosis
Langerhans cell sarcoma
Other dendritic cell neoplasms
Indeterminate dendritic cell tumour
Interdigitating dendritic cell sarcoma

APPENDIX I

Histiocytic neoplasms
- Juvenile xanthogranuloma
- Erdheim-Chester disease
- Rosai-Dorfman disease
- ALK-positive histiocytosis
- Histiocytic sarcoma

Acute leukemias of ambiguous lineage (ALAL)

ALAL with defining genetic abnormalities

Mixed phenotype acute leukemia (MPAL) with *BCR::ABL1* fusion

MPAL with *KMT2A* rearrangement

ALAL with other defined genetic alterations
- Mixed-phenotype acute leukemia with ZNF384 rearrangement
- ALAL with *BCL11B* rearrangement

ALAL, immunophenotypically defined
- MPAL, B/myeloid
- MPAL, T/myeloid
- MPAL, rare types
- ALAL, not otherwise specified
- Acute undifferentiated leukemia

Genetic tumor syndromes with predisposition to myeloid neoplasia

Date of Origin: *May 2010*