

Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

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Next Review: August 2019

Last Review: March 2019

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 hematopoieses following myeloablative doses of chemotherapy.

MEDICAL POLICY CRITERIA

Note: See Appendix II for a glossary of terms.

- I. Allogeneic hematopoietic cell transplant (using either reduced-intensity conditioning [RIC], 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 transplant 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

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.2.2019]:

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

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 (allo-HCT) for the treatment of myeloproliferative neoplasms (MPN; v.2.2019).^[1] 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 2: NCCN Guidelines for Allo-HCT for Myeloproliferative Neoplasms

Prognostic Category	Recommendations for Allo-HCT
Intermediate risk – 1 myelofibrosis IPSS=1 DIPSS-Plus=1 DIPSS=1 or 2	Observation or Ruxolitinib if symptomatic or allo-HCT
Intermediate risk – 2 myelofibrosis IPSS=2 DIPSS-Plus=2 or 3 DIPSS=3 or 4 High-risk myelofibrosis IPSS≥3 DIPSS-Plus=4 to 6 DIPSS=5 or 6	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	Induce remission with hypomethylating agents or intensive induction chemotherapy followed by allo-HCT

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

Hematopoietic cell transplantation (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]) refers to a procedure in which hematopoietic cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole body radiation therapy. Hematopoietic cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “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.

MYELOYDYSPLASTIC SYNDROMES

Myelodysplastic syndromes (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 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 divide patients into 2 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 β 2-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	\geq 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.^[2] 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.^[3]

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 of 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.^[4] 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.^[5]

NOTE:

- 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.^[6] 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.^[7] Other reviews concur with the ASBMT recommendations.^[8-10] 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 32–59 years.^[11] 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 5 months to about 8 years. Grades II-IV acute GVHD varied from 18% to 100%. Relapse risk ranged from a low of 24% at 1 year to 36% at 5 years. Overall survival (OS) 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.

Smaller studies continue to report outcomes from HCT for MDS in variety of patient populations and to evaluate the impact of specific patient, conditioning, and donor characteristics on outcomes.^[12-20]

A growing body of evidence from more than 30 largely heterogeneous uncontrolled studies of reduced intensity conditioning (RIC) with allogeneic HCT shows long-term remissions (i.e., longer than 4 years) can be achieved, often with reduced treatment-related morbidity and mortality, in patients with MDS/AML who otherwise would not be candidates for myeloablative conditioning regimens.^[11,21-36] These prospective and retrospective studies included cohorts of 16–215 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 6–61%. The OS rates ranged between 44% at 1 year to 46% at 5 years, with a median follow-up range of 14 months to over 4 years.

In general, these RIC trials showed a low rate of engraftment failure and low NRM, but at the cost of a higher relapse rate than with myeloablative allogeneic HCT. However, in the absence of prospective, comparative, randomized trials, only indirect comparisons can be made between the relative clinical benefits and harms associated with myeloablative and RIC regimens with allogeneic HCT. Furthermore, no randomized trials have been published in which RIC with allogeneic HCT has been compared with conventional chemotherapy alone, which has been the standard of care in patients with MDS/AML for whom myeloablative chemotherapy and allogeneic HCT are contraindicated. Nonetheless, given the absence of curative therapies for these patients, RIC allogeneic HCT may be a treatment option for patients with MDS who could benefit from allogeneic HCT but who for medical reasons (see Policy Guidelines) would be unable to tolerate a myeloablative conditioning regimen.

MYELOPROLIFERATIVE NEOPLASMS (MPN)

Data on therapy for MPN remain sparse.^[28,30,37] 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.

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.^[38] 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 of the outcomes of 289 patients treated between 1989 and 2002, from the database of the Center for International Bone Marrow Transplant Research (CIBMTR).^[39] The median age was 47 years (range: 18-73 years). Donors were HLA-identical siblings in 162 patients, unrelated individuals in 101 patients, and HLA 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 5-year OS rates were 37%, 30%, and 40%, respectively. DFS rates were 33%, 27%, and 22%, respectively. DFS for patients receiving reduced-intensity transplants was comparable: 39% for HLA identical sibling donors and 17% for unrelated donors at 3 years. In this large retrospective series, allogeneic transplantation for 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.^[31] At a median follow-up of 47 months, the 3-year relapse-free survival was 37% and overall survival was 43%, with a 3-year nonrelapse mortality of 32%.

In a second series, 103 patients (median age 55 years, range 32-68 years) with intermediate to high risk (86% of total patients) 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.^[40] Acute grade II-IV GVHD occurred in 27%, and chronic GVHD in 43% of patients. The cumulative incidence of NRM at 1 year in all patients was 16% (95% confidence interval [CI], 9-23%) but reached 38% (95% CI, 15-61%) among those with a mismatched donor versus 12% (95% CI, 5-19%) among cases with a matched donor (p=0.003). The cumulative relapse rate at 3 and 5 years was 22% (95% CI, 13-31%) and 29% (95% CI, 16-42%), respectively. After a median follow-up of 33 months (range, 12-76 months) 5-year estimated disease-free survival (DFS) and OS was 51% (95% CI, 38-64%) and 67% (95% CI, 55-79%), respectively.

A retrospective study analyzed the impact of conditioning intensity on outcomes of allogeneic HCT in patients with myelofibrosis (MF).^[41] 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 31-60 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 (range 20-89) months, there was a trend for better progression-free survival (PFS) at 3 years in RIC patients compared to myeloablative-conditioned patients (58%, range 23-62 vs. 43%, range 35-76, respectively, p=0.11); there was a similar trend in 3-year OS (68%, range 45-84 vs. 48%, range 27-66, respectively, p=0.08). Non-relapse mortality rates at 3 years trended higher in myeloablative conditioned cases than RIC cases (48%, range 31-74 vs. 27%, range 14-55, respectively, p=0.08). The results of this study suggest that both types of conditioning regimens have curative potential in patients with MF. Despite the RIC patients being significantly older with longer disease duration and poorer performance status than those who received conventional conditioning, the groups had similar outcomes, supporting the use of RIC allogeneic HCT in this population.

In a retrospective study in 9 Nordic transplant centers, a total of 92 patients with MF in chronic phase underwent allogeneic HCT.^[42] Myeloablative (MA) conditioning was given to 40 patients, and RIC was used in 52 patients. The mean age in the 2 groups at transplantation was 46±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 5 years was 49% for the MA-treated patients and 59% in the RIC group ($p=0.125$). Patients treated with RIC experienced significantly less acute GVHD compared with patients treated with MA conditioning ($p<0.001$). The OS at 5 years was 70%, 59% and 41% for patients with Lille score 0, 1 and 2, respectively ($p=0.038$, when age adjustment was made). Twenty-one percent of the patients in the RIC group were given donor lymphocyte infusion because of incomplete donor chimerism, compared with none of the MA-treated patients ($p<0.002$). Nine percent of the patients needed a second transplant because of graft failure, progressive disease or transformation to AML, with no significant difference between the groups.

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.^[43] 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 ($n=34$).^[44] 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 (MDS; v.2.2019) make the following recommendation about hematopoietic cell transplantation (HCT) in general^[45]:

“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.”

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. Use of HCT with or without RIC for the treatment of myelodysplastic syndromes and myeloproliferative neoplasms that does not meet the policy criteria is considered investigational.

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46. BlueCross BlueShield Association Medical Policy Reference Manual "Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms." Policy No. 8.01.21

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
	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
38220	Diagnostic bone marrow; aspiration(s)	
38221	Diagnostic bone marrow; biopsy(ies)	
38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)	
38230	Bone marrow harvesting for transplantation; allogeneic	
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor	
38243		;HPC boost
38242	Allogeneic lymphocyte infusions	
HCPCS J9000–J9999	Chemotherapy drugs code range	
Q0083–Q0085	Chemotherapy administration code range	
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

2016 World Health Organization (WHO) Classification of MDS

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

WHO myeloid neoplasm and acute leukemia classification

Myeloproliferative neoplasms (MPN)

Chronic myeloid leukemia (CML), *BCR-ABL 1+*

Chronic neutrophilic leukemia (CNL)

Polycythemia vera (PV)

Primary myelofibrosis (PMF)

PMF, prefibrotic/early stage

PMF, overt fibrotic stage

Essential thrombocythemia (ET)

Chronic eosinophilic leukemia, not otherwise specified (NOS)

MPN, unclassifiable

Mastocytosis

Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*

Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement

Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement

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Myeloid/lymphoid neoplasms with *FGFR1* rearrangement

Provisional entity: Myeloid/lymphoid neoplasms with PCM1-JAK2

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)

Chronic myelomonocytic leukemia (CMML)

Atypical chronic myeloid leukemia (aCML), *BCR-ABL1*⁻

Juvenile myelomonocytic leukemia (JMML)

MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)

MDS/MPN, unclassifiable

Myelodysplastic syndromes (MDS)

MDS with single lineage dysplasia

MDS with ring sideroblasts (MDS-RS)

MDS-RS and single lineage dysplasia

MDS-RS and multilineage dysplasia

MDS with multilineage dysplasia

MDS with excess blasts

MDS with isolated del(5q)

MDS, unclassifiable

Provisional entity: Refractory cytopenia of childhood

Myeloid neoplasms with germ line predisposition

Acute myeloid leukemia (AML) and related neoplasms

AML with recurrent genetic abnormalities

AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*

AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*

APL with *PML-RARA*

AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*

AML with t(6;9)(p23;q34.1);*DEK-NUP214*

AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*

AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*

Provisional entity: AML with BCR-ABL1

AML with mutated *NPM1*

AML with biallelic mutations of *CEBPA*

Provisional entity: AML with mutated RUNX1

AML with myelodysplasia-related changes

Therapy-related myeloid neoplasms

AML, NOS

AML with minimal differentiation

AML without maturation

AML with maturation

Acute myelomonocytic leukemia

APPENDIX I

Acute monoblastic/monocytic leukemia

Pure erythroid leukemia

Acute megakaryoblastic leukemia

Acute basophilic leukemia

Acute panmyelosis with myelofibrosis

Myeloid sarcoma

Myeloid proliferations related to Down syndrome

Transient abnormal myelopoiesis (TAM)

Myeloid leukemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm

Acute leukemias of ambiguous lineage

Acute undifferentiated leukemia

Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); *BCR-ABL1*

MPAL with t(v;11q23.3); *KMT2A* rearranged

MPAL, B/myeloid, NOS

MPAL, T/myeloid, NOS

B-lymphoblastic leukemia/lymphoma

B-lymphoblastic leukemia/lymphoma, NOS

B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities

B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2); *BCR-ABL1*

B-lymphoblastic leukemia/lymphoma with t(v;11q23.3); *KMT2A* rearranged

B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*

B-lymphoblastic leukemia/lymphoma with hyperdiploidy

B-lymphoblastic leukemia/lymphoma with hypodiploidy

B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*

B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*

Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1-like

Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21

T-lymphoblastic leukemia/lymphoma

Provisional entity: Early T-cell precursor lymphoblastic leukemia

Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma

APPENDIX II: Glossary of Terms used in this Policy

consolidation therapy¹ - 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.

relapse² - The return of a disease or the signs and symptoms of a disease after a period of improvement.

APPENDIX II: Glossary of Terms used in this Policy

salvage therapy³ - Treatment that is given after the cancer has not responded to other treatments.

tandem transplant⁴ – Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

1. NCI Dictionary of Cancer Terms | <https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45654> | Accessed Sep 25 2018
2. NCI Dictionary of Cancer Terms | <https://www.cancer.gov/publications/dictionaries/cancer-terms?CdrID=45866> | Accessed Sep 25 2018
3. NCI Dictionary of Cancer Terms | <https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=44176> | Accessed Sep 25 2018
4. NCCN Guidelines Version 1.2019 Multiple Myeloma | https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf | Accessed Sep 25 2018

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