

# Protocol

## Allogeneic Hematopoietic Stem-Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

(80121)

*(Formerly Allogeneic Stem-Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms)*

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*The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. **Preauthorization is required and must be obtained through Case Management.** Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.*

### Description

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

#### *Background*

##### Hematopoietic Stem-Cell Transplantation

Hematopoietic stem cells may be obtained from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT). 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 stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. 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 HSCT

The conventional ("classical") practice of allogeneic HSCT 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 stem 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 preengraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure

caused by the cytotoxic drugs. Furthermore, in any allogeneic HSCT, 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 HSCT

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 (MA) conditioning treatments. The goal of RIC is to reduce disease burden but also to minimize as much as possible associated treatment-related morbidity and nonrelapse 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 MA to minimally MA with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HSCT 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 Protocol, the term “reduced-intensity conditioning” will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully MA (conventional) regimens.

#### Myelodysplastic Syndromes

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 40–60% of patients, frequently involving deletions of chromosome 5 or 7, or an extra chromosome as in trisomy 8. Signs and symptoms of anemia, often complicated by infections or bleeding, are common in MDS; some patients exhibit systemic symptoms or features of autoimmunity that may be indicative of their disease pathogenesis. The vast majority of MDS diagnoses occur in individuals older than age 55–60 years, with an age-adjusted incidence of approximately 62% among individuals older than age 70 years. Patients either succumb to disease progression to acute myelocytic leukemia (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.

For the past 20 years, the French-American-British (FAB) system has been used to classify MDS into five subtypes as follows: (1) refractory anemia (RA); (2) refractory anemia with ringed sideroblasts (RARS); (3) refractory anemia with excess blasts (RAEB); (4) refractory anemia with excess blasts in transformation (RAEBT); and, (5) chronic myelomonocytic leukemia (CMML). However, the FAB system has been supplanted by that of the World Health Organization (WHO), which records the number of lineages in which dysplasia is seen (unilineage vs. multilineage), separates the 5q-syndrome, and reduces the threshold maximum blast percentage for the diagnosis of MDS from 30% to 20% (see Policy Guidelines for WHO classification scheme for myeloid neoplasms).

Several prognostic scoring systems for MDS have been proposed; the most commonly used is the International Prognostic Scoring System (IPSS). The IPSS groups patients into one of four prognostic categories based on the number of cytopenias, cytogenetic profile, and the percentage of blasts in the bone marrow (see Policy Guidelines). 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, such as peripheral blood counts or blast percentage. However, the IPSS has been useful in comparative analysis of clinical trial results and its utility confirmed at many institutions. A second prognostic scoring system incorporates the WHO subgroup classification that accounts for blast percentage, cytogenetics, and severity of cytopenias as assessed by transfusion requirements. The WHO Classification-based Prognostic scoring system (WPSS) uses a six-category system, which allows more precise prognostication of overall survival (OS) duration, as well as risk for progression to AML. This system, however, is not yet in widespread use in clinical trials.

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-approved hypomethylating agents, nonapproved histone deacetylase inhibitors), immunomodulators (e.g., lenalidomide, thalidomide, antithymocyte globulin, cyclosporine A), low-dose chemotherapy (e.g., cytarabine), and allogeneic HSCT. 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 HSCT is the only approach with curative potential, but its use is governed by patient age, performance status, medical comorbidities, the patient's risk preference, and severity of MDS at presentation.

### Chronic Myeloproliferative Neoplasms

In 2008, a new WHO classification scheme replaced the term chronic myeloproliferative disorder (CMPD) with the term myeloproliferative neoplasms (MPN). These are a subdivision of myeloid neoplasms that includes the four classic disorders: chronic myeloid leukemia (CML), polycythemia vera (PCV), essential thrombocytopenia (ET), and primary myelofibrosis (PMF); the WHO classification also includes chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia/hypereosinophilic syndrome (CEL/HES), mast cell disease (MCD), and MPNs unclassifiable (see Policy Guidelines).

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

As a group, approximately 8400 MPNs are diagnosed annually in the U.S. Like MDS, MPNs primarily occur in older individuals, with approximately 67% reported in patients aged 60 years and older. In indolent, nonprogressing cases, therapeutic approaches are based on relief of symptoms. MA allogeneic HSCT 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 HSCT has extended the potential benefits of this procedure to selected individuals with these disorders.

Chronic myeloid leukemia is considered in a separate Protocol.

### **Policy (Formerly Corporate Medical Guideline)**

Myeloablative allogeneic HSCT may be considered **medically necessary** as a treatment of

- myelodysplastic syndromes (see Policy Guidelines) or
- myeloproliferative neoplasms (see Policy Guidelines).

Reduced-intensity conditioning allogeneic HSCT may be considered **medically necessary** as a treatment of

- myelodysplastic syndromes or
- myeloproliferative neoplasms

in patients who for medical reasons would be unable to tolerate a myeloablative conditioning regimen (see Policy Guidelines).

Myeloablative allogeneic HSCT or reduced-intensity conditioning allogeneic HSCT for myelodysplastic syndromes and myeloproliferative neoplasms that does not meet the criteria in the Policy Guidelines is considered **investigational**.

### Policy Guideline

The myeloid neoplasms are categorized according to criteria developed by the World Health Organization. They are risk-stratified according to the International Prognostic scoring System (IPSS).

#### *2008 WHO Classification Scheme for Myeloid Neoplasms*

1. Acute myeloid leukemia
2. Myelodysplastic syndromes (MDS)
3. Myeloproliferative neoplasms (MPN)
  - 3.1 Chronic myelogenous leukemia
  - 3.2 Polycythemia vera
  - 3.3 Essential thrombocythemia
  - 3.4 Primary myelofibrosis
  - 3.5 Chronic neutrophilic leukemia
  - 3.6 Chronic eosinophilic leukemia, not otherwise categorized
  - 3.7 Hypereosinophilic leukemia
  - 3.8 Mast cell disease
  - 3.9 MPNs, unclassifiable
4. MDS/MPN
  - 4.1 Chronic myelomonocytic leukemia
  - 4.2 Juvenile myelomonocytic leukemia
  - 4.3 Atypical chronic myeloid leukemia
  - 4.4 MDS/MPN, unclassifiable
5. Myeloid neoplasms associated with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1
  - 5.1 Myeloid neoplasms associated with PDGFRA rearrangement
  - 5.2 Myeloid neoplasms associated with PDGFRB rearrangement
  - 5.3 Myeloid neoplasms associated with FGFR1 rearrangement (8p11 myeloproliferative syndrome)

#### *2008 WHO Classification of MDS*

1. Refractory anemia (RA)
2. RA with ring sideroblasts (RARS)

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

#### *Risk Stratification of MDS*

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

#### IPSS: MDS Prognostic Variables

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

#### IPSS: MDS Clinical Outcomes

Risk Group	Total score	Median survival, years	Time for 25% to progress to AML, years
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 or more	0.4	0.2

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

Patients with refractory anemia with or without ringed sideroblasts may be considered candidates for allogeneic HSCT when chromosomal abnormalities are present or the disorder is associated with the development of significant cytopenias (e.g., neutrophils less 500/mm<sup>3</sup>, platelets less than 20,000/mm<sup>3</sup>).

Patients with MPNs may be considered candidates for allogeneic HSCT when there is progression to myelofibrosis, or when there is evolution toward acute leukemia. In addition, allogeneic HSCT may be considered in patients with essential thrombocythemia with an associated thrombotic or hemorrhagic disorder. There are no suitable U.S. Food and Drug Administration (FDA)-approved therapies for these patients, only

supportive care. The use of allogeneic HSCT should be based on cytopenias, transfusion dependence, increasing blast percentage over 5%, and age.

Some patients for whom a conventional myeloablative allogeneic HSCT could be curative may be considered candidates for RIC allogeneic HSCT. These include those patients whose age (typically older than 60 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen. The ideal allogeneic donors are HLA-identical siblings, matched at the HLA-A, B, and DR loci (six of six). Related donors mismatched at one locus are also considered suitable donors. A matched, unrelated donor (MUD) identified through the National Marrow Donor Registry is typically the next option considered. Recently, there has been interest in haploidentical donors, typically a parent or a child of the patient, where usually there is sharing of only three of the six major histocompatibility antigens. The majority of patients will have such a donor; however, the risk of GVHD and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

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

#### MDS

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

#### MPN

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

#### **Benefit Application**

Individual transplant facilities may have their own *additional* requirements or protocols that must be met in order for the patient to be eligible for a transplant at **their** facility.

#### **Medicare Advantage**

If a transplant is needed, we arrange to have the transplant center review and decide whether the patient is an appropriate candidate for the transplant.

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Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to

conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

## References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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