Protocol

Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

(80121)

Medical Benefit		**Effective Date**: 07/01/14	**Next Review Date**: 03/21
Preauthorization	Yes	**Review Dates**: 04/07, 05/08, 09/09, 09/10, 09/11, 07/12, 03/13, 03/14, 03/15, 03/16, 03/17, 03/18, 03/19, 03/20	

Preauthorization is required and must be obtained through Case Management.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. 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.

Populations	Interventions	Comparators	Outcomes
Individuals: • With myelodysplastic syndromes	Interventions of interest are: • Myeloablative or reduced-intensity conditioning allogeneic hematopoietic cell transplant	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Disease-specific survival • Treatment-related mortality • Treatment-related morbidity
Individuals: • With myeloproliferative neoplasms	Interventions of interest are: • Myeloablative or reduced-intensity conditioning allogeneic hematopoietic cell transplant	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Disease-specific survival • Treatment-related mortality • Treatment-related morbidity

DESCRIPTION

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

SUMMARY OF EVIDENCE

For individuals who have MDS or MPN who receive myeloablative conditioning allogeneic HCT, the evidence includes case series, which are often heterogeneous in terms of diseases included. Relevant outcomes are overall survival (OS), disease-specific survival, and treatment-related mortality and morbidity. Primarily uncontrolled, observational studies of HCT for MDS have reported a relatively large range of overall and progression-free survival rates, which reflect the heterogeneity in patient populations, conditioning regimens, and other factors. Reported estimates for three- to five-year OS of 40% to 50% are typical. For HCT for MPN, data are more limited. At least one comparative study of HCT for myelofibrosis has demonstrated improved survival using HCT compared with standard therapy. At present, HCT is the only potentially curative treatment option for patients with MDS and MPN. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have MDS or MPN who receive reduced-intensity conditioning (RIC) allogeneic HCT, the evidence includes primarily retrospective observational series. Relevant outcomes are OS, disease-specific survival, and treatment-related mortality and morbidity. Direct, prospective comparisons of outcomes after HCT with either myeloablative conditioning or RIC in either MDS or MPN are not available. Evidence from retrospective, nonrandomized comparisons have suggested that RIC may be used in patients who are older and have more comorbidities without significantly worsening OS. RIC appears to be associated with lower rates of non-relapse mortality but higher cancer relapse than myeloablative HCT. At present, HCT is the only potentially curative treatment option for patients with MDS and MPN. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

POLICY

Myeloablative allogeneic hematopoietic cell transplantation (allo-HCT) may be considered **medically necessary** as a treatment of

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

Reduced-intensity conditioning allo-HCT 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 allo-HCT or reduced-intensity conditioning allo-HCT for myelodysplastic syndromes and myeloproliferative neoplasms that do not meet the criteria in the Policy Guidelines are considered **investigational**.

POLICY GUIDELINES

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.

MYELOID NEOPLASMS

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

2008 WHO Classification Scheme for Myeloid Neoplasms

1. Acute myeloid leukemia (AML)
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 (see Table 1). 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 based on blast count, degree of cytopenia, and blast percentage. Risk scores were weighted relative to their statistical power. This system is widely used to group patients into either low risk and high-risk groups (see Table 2). The low-risk group includes low-risk and intermediate-1 IPSS groups; treatment goals in low-risk MDS patients are to improve quality of life and achieve transfusion independence. In the high-risk group, which includes intermediate-2 and high-risk IPSS groups, treatment goals are slowing disease progression to 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 worsens by one category change.

Table 1. 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 2. International Prognostic Scoring System: Myelodysplastic Syndrome Clinical Outcomes

Risk Group	Total score	Median survival	Time for 25% of patients to progress to AML
Low	0	5.7 years	9.4 years
Intermediate-1	0.5-1.0	3.5 years	3.3 years
Intermediate-2	1.5-2.0	1.2 years	1.12 years
High	2.5 or more	0.4 years	0.2 years

AML: acute myelocytic leukemia

An updated five category IPSS has been proposed for prognosis in patients with primary MDS or secondary AML to account for chromosomal abnormalities frequently seen in MDS (Schanz et al, 2012). This system stratifies patients into five categories: very poor, poor, intermediate, good, and very good. There has been investigation into using the five category IPSS to better characterize risk in MDS.

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

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

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

Some patients for whom a conventional myeloablative allo-HCT could be curative may be candidates for RIC allo-HCT. They include 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 the use of a standard myeloablative conditioning regimen. The ideal allogeneic donors are human leukocyte antigen (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 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, who usually share three of the six major histocompatibility antigens. Most 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 allo-HCT may be considered for patients as follows:

MDS

- IPSS intermediate-2 or high risk
- Red blood cell transfusion dependence

- Neutropenia
- Thrombocytopenia
- High risk cytogenetics
- Increasing blast percentage

MPN

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

MEDICARE ADVANTAGE

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

BACKGROUND

MYELODYSPLASTIC SYNDROMES

Myelodysplastic syndromes (MDS) can occur as a primary (idiopathic) disease or can be secondary to cytotoxic therapy, ionizing radiation, or other environmental insults. Chromosomal abnormalities are seen in 40% to 60% of patients, frequently involving deletions of chromosome 5 or 7 or an extra chromosome as in trisomy 8. Most MDS diagnoses occur in individuals older than age 55 to 60 years, with an age-adjusted incidence of 62% among individuals older than age 70 years. Patients succumb either to disease progression to acute myeloid 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.

MDS Classification and Prognosis

The French-American-British system was used to classify MDS into five subtypes: (1) refractory anemia; (2) refractory anemia with ringed sideroblasts; (3) refractory anemia with excess blasts; (4) refractory anemia with excess blasts in transformation; and (5) chronic myelomonocytic leukemia. The French-American-British system was supplanted by that of the World Health Organization (WHO), which 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%.

The most commonly used prognostic scoring system for MDS is the International Prognostic Scoring System (IPSS), which 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. This system underweights the clinical importance of severe, life-threatening neutropenia and thrombocytopenia in therapeutic decisions and does not account for the rate of change in critical parameters (e.g., peripheral blood counts, blast percentage). However, the IPSS has been useful in a comparative analysis of clinical trial results and its utility confirmed at many institutions. An updated five-category IPSS has been proposed for prognosis in patients with primary MDS or secondary AML to account for chromosomal abnormalities frequently seen in MDS.[1] This system stratifies patients into five categories: very poor, poor, intermediate, good, and very good. There has been an investigation into using the five-

category IPSS to better characterize risk in MDS. A second prognostic scoring system incorporates the WHO subgroup classification that accounts for blast percentage, cytogenetics, and severity of cytopenias as assessed by transfusion requirements. The WHO classification-based Prognostic Scoring System uses a six-category system, which allows more precise prognostication of overall survival (OS) duration, as well as risk for progression to AML. This system is not yet in widespread use in clinical trials.

MDS Treatment

Treatment of nonprogressing MDS has involved best supportive care, including red blood cell and platelet transfusions and antibiotics. Active therapy was given only when MDS progressed to AML or resembled AML with severe cytopenias. An array of therapies are now available to treat MDS, including hematopoietic growth factors (e.g., erythropoietin, darbepoetin, granulocyte colony-stimulating factor), transcriptional-modifying therapy (e.g., Food and Drug Administration–approved hypomethylating agents, non-approved histone deacetylase inhibitors), immunomodulators (e.g., lenalidomide, thalidomide, antithymocyte globulin, cyclosporine A), low-dose chemotherapy (e.g., cytarabine), and allogeneic hematopoietic cell transplantation (allo-HCT). Given the spectrum of treatments available, the goal of therapy must be decided upfront whether it is to improve anemia, thrombocytopenia, or neutropenia, to eliminate the need for red blood cell transfusion, to achieve complete remission, or to cure the disease.

Allo-HCT is the only approach with curative potential, but its use is governed by patient age, performance status, medical comorbidities, the patient's risk preference, and severity of MDS at presentation. Allo-HCT is discussed in more detail in a subsequent section.

CHRONIC MYELOPROLIFERATIVE NEOPLASMS

Chronic MPN are clonal bone marrow stem cell disorders; as a group, approximately 8,400 MPN are diagnosed annually in the United States. Like MDS, MPN primarily occurs in older individuals, with approximately 67% reported in patients aged 60 years and older.

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

MPN Classification

The WHO (2008) classification scheme replaced the term chronic myeloproliferative disorder with the term myeloproliferative neoplasm. MPN are a subdivision of myeloid neoplasms that includes four classic disorders: chronic myeloid leukemia, polycythemia vera, essential thrombocytopenia, and primary myelofibrosis. The WHO classification also includes chronic neutrophilic leukemia, chronic eosinophilic leukemia/hypereosinophilic syndrome, mast cell disease, and MPN unclassifiable.

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.

The Food and Drug Administration (2011) approved the orally administered selective Janus kinase 1 and 2 inhibitor ruxolitinib for the treatment of intermediate- or high-risk myelofibrosis. Ruxolitinib has been associated with improved OS, spleen size, and symptoms of myelofibrosis compared with placebo.[2] The COMFORT-II trial (2013) compared ruxolitinib with best available therapy in patients who had intermediate- and high-risk myelofibrosis,

and demonstrated improvements in spleen volume and OS.[3] In a randomized trial comparing ruxolitinib with best available therapy (including antineoplastic agents, most commonly hydroxyurea, glucocorticoids) with no therapy for treatment of myelofibrosis, Harrison et al (2012) reported improvements in spleen size and quality of life, but not OS.[4]

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

HEMATOPOIETIC CELL TRANSPLANTATION

Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allo-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 "naive" and thus are associated with a lower incidence of rejection or graft-versus-host disease. Cord blood is discussed in greater detail in the Placental and Umbilical Cord Blood as a Source of Stem Cells Protocol.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is critical for achieving a good outcome of allo-HCT. Compatibility is established by typing of human leukocyte antigen (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 allo-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 of this procedure is due to a combination of initial eradication of malignant cells and a subsequent graft-versus-malignancy effect that develops after engraftment of allogeneic stem cells within the patient's bone marrow space. While the slower graft-versus-malignancy 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 events 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 allo-HCT, immune suppressant drugs are required to minimize graft rejection and graft-versus-host disease, which also increases the susceptibility of the patient to opportunistic infections.

Reduced-Intensity Conditioning (RIC) for Allo-HCT

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 and to minimize as much as possible associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of non-relapse mortality 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, and intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant

cells. For this evidence review, RIC will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

REGULATORY STATUS

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

RELATED PROTOCOLS

Hematopoietic Cell Transplantation for Acute Myeloid Leukemia

Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia

Placental and Umbilical Cord Blood as a Source of Stem Cells

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

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

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