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

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for allogeneic hematopoietic stem-cell transplantation for myelodysplastic and myeloproliferative neoplasms when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Allogeneic hematopoietic stem-cell transplantation (HSCT) may be considered medically necessary as a treatment of:
- myelodysplastic syndromes (see Considerations) or
- myeloproliferative neoplasms (see Considerations).

In patients who for medical reasons would be unable to tolerate a myeloablative conditioning regimen, reduced-intensity conditioning allogeneic HSCT may be considered medically necessary as a treatment of:
- myelodysplastic syndromes (see Considerations) or
- myeloproliferative neoplasms (see Considerations)

When Policy Topic is not covered
Allogeneic stem-cell transplantation for myelodysplastic and myeloproliferative neoplasms is not covered if the criteria are not met.

Considerations
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 PDGFRα, PDGFRβ, or FGFR1
   5.1. Myeloid neoplasms associate with PDGFRα rearrangement
   5.2. Myeloid neoplasms associate with PDGFRβ rearrangement
   5.3. Myeloid neoplasms associate 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 7 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.

<table>
<thead>
<tr>
<th>Variable: MDS Prognostic Variables</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow blasts (5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karyotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytopenias</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow blasts (5)</td>
<td>&lt; 5</td>
<td>5-10</td>
<td>11-20</td>
<td>21-30</td>
<td></td>
</tr>
<tr>
<td>Karyotype</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytopenias</td>
<td>0/1</td>
<td>2/3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable: MDS Clinical Outcomes</th>
<th>Total score</th>
<th>Median survival, yrs</th>
<th>Time for 25% to progress to AML, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Group</td>
<td>Total score</td>
<td>Median survival, yrs</td>
<td>Time for 25% to progress to AML, years</td>
</tr>
<tr>
<td>Low</td>
<td>0</td>
<td>5.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>0.5-1.0</td>
<td>3.5</td>
<td>3.3</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>1.5-2.0</td>
<td>1.2</td>
<td>1.12</td>
</tr>
<tr>
<td>High</td>
<td>2.5 or more</td>
<td>0.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

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/mm3, platelets less than 20,000/mm3).

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 allotransplant 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 (6 of 6). 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 3 of the 6 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

Reimbursement for Stem Cell collection and storage are considered payable under the Transplant Benefit when billed as a one-time, all-inclusive charge.

**Transplant Benefit**
The date on which the Transplant Benefit starts accumulating is determined by the transplant coordinator. The Transplant Benefit ends when the Transplant Lifetime Maximum benefit (if applicable) has been exhausted.

Benefits include:
- hospitalization of the recipient for medically recognized transplants from a donor to a transplant recipient;
- evaluation tests requiring hospitalization to determine the suitability of both potential (member's benefits must be verified with regard to the potential donor who does not turn out to be the actual donor) and actual donors, when such tests cannot be safely and effectively performed on an
outpatient basis (Note: The member's benefits must be verified with regard to the potential donor who does not turn out to be the actual donor.);

- hospital room, board and general nursing in semi-private rooms;
- special care units, such as coronary and intensive care;
- hospital ancillary services;
- physicians' services for surgery, technical assistance, administration of anesthetics, and medical care;
- acquisition, preparation, transportation, and storage of organ / tissue / cells;
- diagnostic services;
- drugs which require a prescription by federal law;
- medical and surgical care of the donor (related to the procurement of the organ / tissue / cells) if coverage is not available to the donor from any other source. (Covered services provided to a donor will be applied against the recipient's transplant maximum benefit, if applicable)

If the donor and recipient are both listed on the same (family) policy, BCBSKC charges only one deductible and one coinsurance, if applicable.

In addition to the specific organ criteria, transplant candidates must also meet the following general criteria, including, but not limited to:

- Since compliance is a major factor in transplant graft survival, the patient (or legal guardian) must have the ability to accept and understand the transplant procedure and to maintain compliance with long-term medical management and immunosuppression.
- If applicable, patients with a history of malignancy must have passed the recommended length of time to be considered cured for that specific cancer. A complete metastatic evaluation must be performed before a patient will be considered an acceptable transplant candidate.
- Patients with a history of alcohol or substance abuse must have a six month history of abstinence as evidenced by negative urine or serum drug screens taken randomly.
- The patient must have adequate cardiopulmonary status.
- The patient must be free from active infection.

A covered person is eligible for retransplantation as deemed medically necessary and appropriate by BCBSKC. Review of a retransplantation request will include review of the covered person's compliance with relevant transplant selection criteria including, but not limited to, adherence to medication regimens, follow-up examinations and abstinence from the use of alcohol and drugs.

Clinical trials for conditions other than those allowed in this policy may be available in the research setting. However, these trials are considered investigational and/or experimental and therefore contract exclusions.

Note: There are some state mandates in place that require insurance carriers to cover certain clinical trials under very specific guidelines. Please contact your BCBSKC representative for more information.

**Description of Procedure or Service**

**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). Cord blood is discussed in greater detail in a separate policy.

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 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 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 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 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 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 (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. 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 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.

For the past 20 years, the French-American-British (FAB) system has been used to classify MDS into 5 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 versus 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 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 WPSS uses a 6-category system which allows more precise prognostication of overall survival 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 Considerations section).

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, 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 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 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 policy.

Rationale
Myelodysplastic Syndromes (MDS)

Despite the successes seen with new drugs now available to treat MDS (e.g., decitabine, azacitidine, lenalidomide), allogeneic HSCT using myeloablative (MA) 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. A majority of patients (n=885) received matched related donor (MRD) allogeneic HSCT, 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, 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 approximately 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 between 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. Hematopoietic stem-cell transplantation HSCT is the only treatment capable of complete and permanent eradication of the MDS clone.

Evidence from a number of largely heterogeneous, uncontrolled studies of reduced-intensity conditioning (RIC) with allogeneic HSCT shows long-term remissions (i.e., longer than 4 years) can be achieved, often with reduced treatment-related morbidity and mortality, in patients with myelodysplastic syndromes/acute myelocytic leukemia (MDS/AML) who otherwise would not be candidates for MA conditioning regimens. These prospective and retrospective studies included cohorts of 16–215 patients similar to those in the MA allogeneic HSCT studies. The most common conditioning regimens used were fludarabine-based, with cyclosporine (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 2013, Kim and colleagues published a randomized phase III trial to compare the toxicities of two different conditioning regimens (reduced cyclophosphamide [Cy], fludarabine, and anti-thymocyte globulin [ATG]; standard Cy-ATG). Four (of 83) patients had MDS, and the remaining study patients had severe aplastic anemia. Overall, the incidence of toxicities were reported to be lower in patients receiving the reduced conditioning regimen (23% vs. 55%; p = 0.003). Subgroup analyses showed no differences in the overall results based on differential diagnosis. 

In general, these RIC trials showed a low rate of engraftment failure and low non-relapse mortality (NRM) but at the cost of a higher relapse rate than with MA allogeneic HSCT. 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 (MA) and RIC regimens with allogeneic HSCT. Furthermore, no randomized trials have been published in which RIC with allogeneic HSCT has been compared with conventional chemotherapy alone, which has been the standard of care in patients with MDS/AML for whom MA chemotherapy and allogeneic HSCT are contraindicated. Nonetheless, given the absence of curative therapies for these patients, coupled with clinical input (see below), RIC allogeneic HSCT may be considered medically necessary for patients with MDS who could benefit from allogeneic HSCT but who for medical reasons (see Policy Guidelines) would be unable to tolerate a MA conditioning regimen.

The recommendations of a systematic review of the role of allogeneic HSCT in patients with MDS prepared by the American Society for Blood and Marrow Transplantation (ASBMT) agree with the present policy statements. (15) Other recent reviews concur with the ASBMT recommendations. (16-21)
**Myeloproliferative Neoplasms (MPN)**

Data on therapy for MPN remain sparse. (10, 22, 23) As outlined previously in this policy, with the exception of MA chemotherapy and allogeneic HSCT, no therapy has yet been proven to be curative or to prolong survival of patients with MPN. However, the significant toxicity of MA conditioning and allogeneic HSCT in MPN has led to study of RIC regimens for these diseases. One recent series included 27 patients (mean age: 59 years) with MPN who underwent allogeneic HSCT using an RIC regimen of low-dose (2 Gy) total-body irradiation alone or with the addition of fludarabine. (8) At a median follow-up of 47 months, the 3-year relapse-free survival was 37%, and OS was 43%, with a 3-year NRM 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 thrombocytopenia (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 HSCT from related (n=33) or unrelated (n=70) donors. (24) 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.

The largest study of allogeneic HSCT for primary myelofibrosis comes from 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). (25) 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.

Data from direct, prospective comparison of outcomes of MA conditioning and allogeneic HSCT versus RIC and allogeneic stem-cell support in MPN are not available. However, a recent retrospective study analyzed the impact of conditioning intensity on outcomes of allogeneic HSCT in patients with myelofibrosis (MF). (26) This multicenter trial included 46 consecutive patients treated at 3 Canadian and 4 European transplant centers between 1998 and 2005. Twenty-three patients (median age 47 years, range 31-60 years) underwent MA conditioning, and 23 patients (median age 54 years, range 38-74 years) underwent RIC. The majority in both groups (85%) were deemed intermediate- or high-risk. At a median follow-up of 50 months (range 20-89), there was a trend for better progression-free survival (PFS) at 3 years in RIC patients compared to MA-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). NRM rates at 3 years trended higher in MA 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 HSCT in this population.

In a retrospective study in 9 Nordic transplant centers, a total of 92 patients with MF in chronic phase underwent allogeneic HSCT. (27) 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.

**Ongoing Clinical Trials**

A search of the National Cancer Institute (NCI) Clinical Trials Database http://www.cancer.gov/clinicaltrials/search/results?protocolsearchid=9718439. In addition, a search of online site NCI clinical trials database in October 2013 identified 8 active Phase III trials that involve stem-cell support for patients with MDS/AML or MPN. Information on these trials can be accessed via the following link, available online at: ClinicalTrials.gov identified numerous Phase II trials of various treatments for these diseases which are actively recruiting patients.

**Clinical Input Received through Physician Specialty Societies and Academic Medical Centers**

In response to requests, input was received from two Academic Medical Center specialists prior to review for May 2009. While the various Physician Specialty Societies and Academic Medical Centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the Physician Specialty Societies or Academic Medical Centers, unless otherwise noted.

There was consensus among reviewers that RIC allogeneic HSCT was of value in patients with MDS or MPN who would be medically unable to tolerate a MA HSCT.

**Summary**

Hematopoietic stem cell transplantation (HSCT) is at present the only potentially curative treatment option for patients with myelodysplastic syndromes and myeloproliferative neoplasms. The absence of other curative therapies coupled with clinical data and input permit the conclusion that allogeneic HSCT using either a myeloablative or reduced-intensity conditioning regimen is medically necessary in appropriately selected patients with these conditions. Patient selection is guided by age and disease risk factors, as outlined in the Policy Guidelines.

**Practice Guidelines and Policy Statements**

**National Comprehensive Cancer Network Guidelines**

The 2014 National Comprehensive Cancer Network (NCCN) treatment guidelines (v.2.2014) for the use of allogeneic HSCT indicate this procedure is preferred at diagnosis in patients who are candidates for high-intensity therapy, have a suitable donor, and have de novo MDS classified as IPSS Int-2 and High, or those who have de novo MDS classified as Int-1 with severe cytopenias unresponsive to standard therapies (available online at: http://www.nccn.org/professionals/physician_gls/pdf/mds.pdf). Reduced-intensity or MA conditioning may be used based on patient age, performance status, comorbid conditions, psychosocial status, patient preference, and availability of caregiver. MRD cells are preferred, but MUD cells are an option at some centers. The role of pretransplant remission induction using intensive chemotherapy has not been established.

References


Billing Coding/Physician Documentation Information

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38204</td>
<td>Management of recipient hematopoietic progenitor cell donor search and cell acquisition</td>
</tr>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogenic</td>
</tr>
<tr>
<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing</td>
</tr>
<tr>
<td>38209</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing</td>
</tr>
<tr>
<td>38210</td>
<td>Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion</td>
</tr>
<tr>
<td>38211</td>
<td>Transplant preparation of hematopoietic progenitor cells; tumor cell depletion</td>
</tr>
<tr>
<td>38212</td>
<td>Transplant preparation of hematopoietic progenitor cells; red blood cell removal</td>
</tr>
<tr>
<td>38213</td>
<td>Transplant preparation of hematopoietic progenitor cells; platelet depletion</td>
</tr>
<tr>
<td>38214</td>
<td>Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion</td>
</tr>
<tr>
<td>38215</td>
<td>Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer</td>
</tr>
<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
</tr>
<tr>
<td>38240</td>
<td>Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic</td>
</tr>
<tr>
<td>86812</td>
<td>HLA typing; A, B, or C (eg, A10, B7, B27), single antigen</td>
</tr>
<tr>
<td>86813</td>
<td>HLA typing; A, B, or C, multiple antigens</td>
</tr>
<tr>
<td>86816</td>
<td>HLA typing; DR/DQ, single antigen</td>
</tr>
<tr>
<td>86817</td>
<td>HLA typing; DR/DQ, multiple antigens</td>
</tr>
<tr>
<td>86821</td>
<td>HLA typing; lymphocyte culture, mixed (MLC)</td>
</tr>
<tr>
<td>86822</td>
<td>HLA typing; lymphocyte culture, primed (PLC)</td>
</tr>
<tr>
<td>S2150</td>
<td>Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and post-transplant care in the global definition</td>
</tr>
</tbody>
</table>

Additional Policy Key Words

N/A

Policy Implementation/Update Information

12/1/01 New policy. Added to Surgery and Lab sections.
12/1/02 No policy statement change. Added new codes
12/1/03 No policy statement change.
12/1/05  No policy statement change. Removed from Lab section.
4/1/06  Considerations section revised to include general criteria.
12/1/06  No policy statement changes.
12/1/07  No policy statement changes.
12/1/08  “Myeloproliferative” added and “High-Dose Chemotherapy” removed from policy title and policy statements reworded, but the policy statements remain otherwise unchanged.
12/1/09  Policy statements revised to indicate that RIC HSCT may be considered medically necessary as a treatment of myelodysplastic syndrome and myeloproliferative neoplasms in patients who for medical reasons would be unable to tolerate a myeloablative conditioning regimen. Term “Myeloproliferative Disorders” replaced with “Myeloproliferative Neoplasms” in title and text.
12/1/10  No policy statement changes.
12/1/11  No policy statement changes.
1/1/12  Coding updated.
12/1/12  No policy statement changes.
12/1/13  Minor changes in the description. Added to title name. No policy statement changes.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.