Cigna Medical Coverage Policy

Subject **Stem-Cell Transplantation for Myelodysplastic Syndromes**

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Coverage Policy

Cigna covers allogeneic hematopoietic stem-cell transplantation (HSCT) as medically necessary for the treatment of an individual with intermediate- or high-risk myelodysplastic syndrome (MDS) who has an appropriately-matched HLA donor.

Cigna covers autologous HSCT as medically necessary for the treatment of intermediate- or high-risk MDS when ALL of the following criteria are met:

- The individual is in complete remission
- The individual is not a candidate for allogeneic HSCT
- An appropriately-matched HLA donor is not available

General Background

The myelodysplastic syndromes (MDS) are a heterogeneous group of disorders characterized by peripheral blood cytopenias secondary to bone marrow dysfunction (National Cancer Institute [NCI], 2012). The syndromes may arise de novo, or secondarily after treatment with chemotherapy and/or radiation therapy for other

diseases. Secondary myelodysplasia usually has a poorer prognosis (NCI, 2012) and primarily affects adults ≥ age 60 with a two-year overall survival of <20% with advanced MDS (Kindwall-Keller, 2009). Although rare in children and young adults, MDS has an aggressive clinical course in these subgroups.

Prognosis is directly related to the number of bone marrow blast cells and to the amount of peripheral blood cytopenias. Independent adverse factors include poor performance, older age, thrombocytopenia, anemia, increased bone marrow blasts, leukocytosis, certain chromosome abnormalities, and earlier transfusions (Kindwall-Keller, 2009, Faderl, 2008; NCI, 2012). In a large percentage of cases, the syndromes progress to overt acute myeloid leukemia (DeAngelo, 2008).

Several classification systems have been developed to determine prognosis and guide treatment, including the French-American-British (FAB) system, the World Health Organization (WHO), WHO Prognostic Scoring System (WPSS), and the International Prognostic Scoring System (IPSS), based on bone marrow blast percentage, number of peripheral blood cytopenias, and cytogenetic subgroup. The IPSS system has been used to assign patients to prognostic risk groups in terms of survival and evolution to acute myelogenous leukemia: Low, Intermediate-1, Intermediate -2, and High risk, while the WPSS classifies patients into five prognostic groups: Very Low, Low, Intermediate, High, and Very High.

Hematopoietic stem-cell transplantation (HSCT) has been proposed as a treatment option for selected individuals with intermediate-or high-risk MDS.

Stem-Cell Transplantation
Stem-cell transplantation refers to the transplantation of hematopoietic stem cells (HSCs) into an individual. HSCT can be either autologous (using the person's own stem cells) or allogeneic (using stem cells from a donor).

Transplantation outcome in patients with MDS is related to disease stage (marrow myeloblast count), prognostic score (IPSS), cytogenetic findings, possibly remission status before transplantation, iron overload, source of stem cells, co-morbid conditions, and preparative regimen. The selection of an appropriately-matched allogeneic donor source is dependent on several variables including the availability of a human leukocyte antigen (HLA)-identical sibling donor, and stage of disease. It is preferable for donors to have an HLA type that is identical to the recipient due to the potential for increased complications such as graft rejection and graft-versus-host disease; however, only about one-third of individuals who might otherwise be eligible for allogeneic HSCT have an HLA-matched sibling donor. Especially for individuals with high-risk disease, additional appropriate donor sources may include HLA-matched unrelated and HLA partially-matched related donors.

In early clinical trials, transplantation success showed a strong inverse correlation with patient age. Age continues to be a relevant factor; the development of reduced intensity nonmyeloablative conditioning strategies has further attenuated the impact of age (Scott, 2008).

There is ongoing discussion regarding the most appropriate timing for HSCT. At present, data suggest that selected individuals with the International Prognostic Scoring System (IPSS) intermediate-2 and high-risk myelodysplastic syndromes (MDS) may benefit from immediate hematopoietic stem-cell transplantation (HSCT) while those with IPSS low- and intermediate-1-risk groups may improve overall survival by delay of HSCT until disease progression (Kindwall-Keller, 2009, Alessandrino, 2008).

A boost of hematopoietic progenitor or stem cells, also referred to as a hematopoietic stem-cell infusion (HSCI) may be used to facilitate more rapid hematopoietic recovery, graft loss, or loss of chimerism following HSCT. The cell product used for a boost may be a previously cryopreserved cell product that contains stem cells or may alternatively require the donor to undergo additional evaluation, mobilization, and harvest. A boost is not preceded by a preparative regimen, and may be required when additional conventional chemotherapy is given to treat relapse and reestablish remission after transplantation. Prolonged cytopenias and immunosuppression may result, requiring additional HSCI which is typically given days to weeks after reinduction chemotherapy (LeMaistre, 2013).

Contraindications
Many factors affect the outcome of a tissue transplant; the selection process is designed to obtain the best result for each individual. Overall health, age and disease stage are extremely important considerations in

evaluating transplant candidates. The presence of any significant co-morbid condition that would significantly compromise clinical care and chances of survival is a contraindication to transplant. Relative contraindications may include, but are not limited to:

- poor cardiac function (ejection fraction < 45%)
- poor liver function (bilirubin > 2.0mg/dl and transaminases greater than two times normal), unless related to acute myelogenous leukemia (AML)
- poor renal function (creatinine clearance < 50ml/min)
- poor pulmonary function (diffusion capacity [DLCO] < 60% of predicted)
- active central nervous system involvement
- a pattern of demonstrated noncompliance which would place a transplant at serious risk of failure
- presence of human immunodeficiency virus OR an active form of any ONE of the following:
    - hepatitis B virus (HBV)
    - hepatitis C virus (HCV)
    - human T-cell lymphotropic virus (HTLV)-1
- Karnofsky rating < 60% and/or Eastern Cooperative Oncology Group (ECOG) performance status > 2

Allogeneic HSCT: According to the National Comprehensive Cancer Network® [NCCN®], 2014), high intensity therapies, including hematopoietic stem-cell transplantation (HSCT) can potentially change the natural course of the disease; although there is an increased risk of regimen-related morbidity and mortality. Nonetheless, myeloablative conditioning followed by allogeneic HSCT is considered a preferred treatment approach for a subset of individuals with myelodysplastic syndromes (MDS), particularly those with high-risk disease (NCCN®, 2014). According to the NCI (2012), allogeneic HSCT offers the potential for long-term disease-free survival (DFS), and is a component of the standard of care for individuals with good performance status and no significant comorbidity for individuals with de novo and secondary myelodysplastic syndromes. There are limited randomized controlled trial data comparing high-dose chemotherapy and hematopoietic stem-cell transplantation (HSCT) with standard dose chemotherapy.

Literature Review
Prospective and retrospective case studies suggest that 20% to 40% of patients with high-risk disease can experience long-term disease-free survival (DFS) after allogeneic transplantation from a matched donor (DeAngelo, 2008). Whether transplantation should be performed before or after patients achieve remission after induction chemotherapy has not been established; however, individuals who receive allogeneic HSCT while in complete remission tend to have better outcomes than those who are transplanted with residual disease (Alessandrino, 2008; Kebriaei, 2005; Scott, 2005). Advanced age is associated with a higher incidence and severity of post-transplantation complications; nonetheless there is some evidence that allogeneic HSCT is feasible in persons up to age 70 (DeAngelo, 2008; Wallen, 2005).

Reduced intensity or non-myeloablative preparative regimens have been suggested as treatment for selected patients, typically those with co-morbid medical conditions or older individuals who cannot tolerate the treatment-related effects of intensive therapy. These are designed to reduce regimen-related toxicities and to utilize the graft-versus-leukemia/graft-versus-myelodysplasia effect of the infused donor lymphocytes (de Witte, 2007).

Although relapse rates are higher with non-myeloablative conditioning, treatment-related mortality is higher with more intensive chemotherapy, with similar overall survival rates for both therapies. Randomized control trial data is scarce; however, several prospective case series and retrospective analyses have demonstrated similar disease-free and overall survival rates with myeloablative and non-myeloablative/reduced-intensity conditioning regimens. Two-, three-, and four-year overall survival rates are 33% versus 35%, 39% versus 33%, and 36% versus 27%, respectively, for individuals undergoing allogeneic HSCT with myeloablative or non-myeloablative/reduced-intensity therapy (Luger, 2012; Flynn, 2007; Martino, 2006; de Witte, 2001).

Summary for Allogeneic HSCT: Allogeneic HSCT has the potential to change the course of this disease. It is considered a preferred treatment for selected individuals with intermediate- or high-risk myelodysplastic syndromes (MDS).

Autologous HSCT: Autologous HSCT provides an alternative stem-cell source for individuals who do not have a human leukocyte antigen (HLA)-identical donor, and may be used in older individuals as the conditioning regimens are less toxic than those for allogeneic HSCT (de Witte, 2006). The rationale for the use of autologous HSCT in MDS is the feasibility of collecting normal stem cells at the time of chemotherapy-induced remission (Alessandrino, 2002).

Literature Review
In a retrospective study, Kroger et al. (2006) reported the results of 65 persons with treatment-related MDS/acute myelogenous leukemia (AML) who received an autologous HSCT. The Kaplan-Meier probabilities of five-year overall and disease-free survival were 35 and 32%, respectively. The cumulative incidence of relapse was 58%, and the transplant-related mortality (TRM) was 12%. In a multivariate analysis, transplantation in first complete remission and presence of younger age influenced OS. Although data are not robust, autologous HSCT is considered an appropriate treatment option for selected individuals with intermediate- or high-risk MDS.

Summary for Autologous HSCT: Autologous HSCT may be appropriate in carefully selected individuals who achieve a complete remission following induction chemotherapy and in whom suitable autologous stem-cells can be collected. Outcomes with autologous HSCT appear comparable to allogeneic transplantation protocols that utilize donors other than HLA-identical siblings and phenotypically-identical family members.

Professional Societies/Organizations
National Cancer Institute (NCI): The NCI (2012) notes that allogeneic HSCT is the only potentially curative treatment for MDS, although the relatively high morbidity and mortality of this approach limits its use. Allogeneic stem cell transplantation with reduced-intensity conditioning (RIC) has extended transplantation as a possible modality for treatment of older patients.

National Comprehensive Cancer Network Guidelines™ (NCCN Guidelines™): The NCCN (2014) notes that timing of transplantation has not been established (e.g., before or after patients achieve remission after induction chemotherapy). Allogeneic HSCT from a human leukocyte antigen (HLA)-matched sibling donor is a preferred approach for treating a portion of patients with myelodysplastic syndromes (MDS), particularly those with high-risk disease. Matched nonmyeloablative transplant regimens and matched unrelated donor stem-cell transplants are becoming options at some centers. In addition, the NCCN notes that autologous bone marrow or peripheral blood stem cell transplantation is being considered in some investigative settings.

Therapy for lower-risk patients (i.e., IPSS Low, Intermediate-1, WPSS Very low, Low, and Intermediate) who do not respond to treatment may include allogeneic HSCT. Regarding therapy for higher risk patients (i.e., IPSS Intermediate-2, High, or WPSS High, Very High) the NCCN notes the first choice of a donor has remained an HLA-matched sibling, although results with HLA matched unrelated donors are comparable to those obtained with HLA-matched siblings. With the increasing use of cord blood or HLA haploidentical related donors HSCT has become a viable option for many patients. High dose conditioning is generally used for younger patients, whereas the approach using reduced/low intensity conditioning for HSCT is generally the strategy used in older individuals. Autologous HSCT is being evaluated in some centers.

American Society for Blood and Marrow Transplantation (ASBMT): The Guideline titled “The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Therapy of Myelodysplastic Syndromes” notes that early stem-cell transplantation is recommended for patients with an International Prognostic Scoring System (IPSS) score of INT-2, considered high risk, at diagnosis who have a suitable donor and meet the transplanting center’s eligibility criteria, and for selected patients at low risk (IPSS score of INT-1) at diagnosis who have poor prognostic features not included in the IPSS (e.g., older age, refractory cytopenias). A human-leukocyte antigen (HLA)-matched allogeneic donor (i.e., sibling, other family member, unrelated individual, or cord blood) stem-cell transplantation is recommended if an appropriate donor is available. If an allogeneic donor is not available, and complete remission is achieved with induction therapy, then an autologous stem-cell transplant can be considered in the context of a clinical trial (2009).

National Marrow Donor Program (NMDP)/American Society of Bone Marrow Transplantation (ABST): In guidelines published jointly by the NMDP and the ASBMT (2014), a transplant consultation is recommended for individuals with an intermediate or high IPSS score, or any MDS with poor prognostic features, including treatment-related MDS, refractory cytopenias, adverse cytogenetics, or transfusion dependence.

Use Outside of the US: European LeukemiaNet ([ELN], 2013): On behalf of the ELN Malcovati et al. published guidelines regarding the diagnosis and treatment of primary myelodysplastic syndromes in adults. The Guidelines note that fit patients up to age 65 to 70 years with IPSS intermediate-2 or high risk and those with IPSS intermediate-1 risk with excess blasts or poor-risk cytogenetics are candidates for allogeneic SCT. No specific recommendation was given on the best myeloablative conditioning regimen. The Guidelines note for MDS patients with a contraindication to a standard myeloablative preparative regimen due to comorbidity, reduced intensity conditioning allogeneic SCT should be considered, preferably within a clinical trial. Regarding autologous HSCT, ELN notes that no recommendations can be given at present on the use of autologous SCT for patients without a suitable donor who are receiving intensive chemotherapy.

European Society of Medical Oncology ([ESMO], 2010): On behalf of the ESMO Fey et al. published clinical practice guidelines for diagnosis, treatment and follow-up for acute myeloblastic leukaemias and myelodysplastic syndromes in adult patients. The Guidelines note that consolidation therapy is warranted once patients have reached clinical and haematological remission. Patients with higher-risk MDS with a human leukocyte antigen (HLA)-identical sibling are candidates for allogeneic HSCT, provided their age and performance status allow for such treatment. Individuals in these risk groups without a family donor may qualify for allogeneic HSCT with an HLA -matched unrelated donor. Haploidentical donors may be considered in an individual when a killer-immunoglobulin-like receptor (KIR) mismatch is present. The role of high-dose chemotherapy with autologous stem cell retransfusion is controversial.

Summary
The myelodysplastic syndromes (MDS) include an array of stem cell disorders characterized by peripheral blood cytopenias and variable risks of leukemic transformation. Although data are not robust, the published, peer-reviewed scientific literature supports the safety and effectiveness of hematopoietic stem-cell transplantation (HSCT) for the treatment of selected individuals with MDS. Additionally, there is professional society consensus support for this therapy as noted in published clinical practice guidelines.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Covered when medically necessary:

CPT®* Codes	Description
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in

	plasma, mononuclear, or buffy coat layer
38230	Bone marrow harvesting for transplantation, allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation, per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
38242	Allogeneic lymphocyte infusions

HCPCS Codes	Description
S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood-derived stem-cell transplantation, allogeneic
S2150	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 or of pre-and post-transplant care in the global definition

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