Cigna Medical Coverage Policy

Subject **Stem-Cell Transplantation for Aplastic Anemia and Fanconi Anemia**

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Coverage Policy

Cigna covers allogeneic hematopoietic stem-cell transplantation (HSCT) from an appropriately-matched human leukocyte antigen (HLA) donor as medically necessary for the treatment of EITHER of the following conditions:

- severe aplastic anemia (AA)
- Fanconi anemia

General Background

Aplastic anemia, along with Diamond-Blackfan anemia, Fanconi anemia, and other anemias, is a bone marrow failure syndrome (IBMFS). IBMFS are rare disorders in which there is usually some form of aplastic anemia (failure of the bone marrow to produce blood). Some of these conditions have typical changes in physical appearance or in laboratory findings which suggest a specific diagnosis. Failure of the bone marrow to produce blood cells predisposes an individual to the future development of other hematological disorders, including leukemia and myelodysplastic syndrome. Hematopoietic stem-cell transplantation (HSCT) has been proposed for the treatment of these syndromes.

Stem-Cell Transplantation

Stem-cell transplantation refers to the transplantation of hematopoietic stem cells (HSCs) from a donor into a recipient. HSCs are immature cells that can develop into any of the three types of blood cells (i.e., red cells, white cells or platelets). Allogeneic HSCT uses stem cells from a donor.

In allogeneic HSCT it is preferable for donors to have a human leukocyte antigen (HLA) type that is identical to the recipient. Matching is performed on the basis of variability at three of more loci of the HLA gene (e.g., HLA-A, HLA-B, HLA-DRB1). Alternative donor sources are being evaluated for individuals with aplastic anemia and Fanconi anemia who do not have an HLA-identical donor. As HLA variability increases, transplant-related morbidity and mortality, including graft rejection and graft-versus-host disease, also increase. Long-term survival after mismatched related donation is inferior to genotypically matched donor transplantation (Young, 2008).

Contraindications to Stem-Cell Transplantation
The presence of any significant co-morbid conditions which would significantly compromise clinical care and chances of survival is a contraindication to transplantation. Relative contraindications to HSCT include, but are not limited to:

- poor cardiac function (ejection fraction less than 45%)
- poor liver function (bilirubin greater than 2.0 mg/dL and transaminases greater than two times normal)
- poor renal function (creatinine clearance less than 50 mL/min)
- poor pulmonary function (diffusion capacity [DLCO] less than 60% of predicted)
- presence of human immunodeficiency virus or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus (HTLV-1)
- Karnofsky rating less than 60% and/or Eastern Cooperative Oncology Group (ECOG) performance status greater than two

Aplastic Anemia
Aplastic anemia (AA), also called hypoplastic anemia, is a potentially fatal bone marrow failure disorder that is characterized by pancytopenia and a hypocellular bone marrow (DeZern, 2012). This failure, which can be congenital or acquired, is related to either a defect in the stem-cell pool, or an injury to the microenvironment that supports the bone marrow. Immunosuppression improves marrow function in up to 80% of individuals with AA; however, it is not uncommon for those who respond to immunosuppressive therapy to experience disease relapse. Aplastic anemia is classified as non-severe (NSAA), severe (SAA) and very severe based on the degree of the peripheral blood cytopenias.

Severe AA is diagnosed according to the following criteria (Young, 2005):

- No other hematologic disease
- Bone marrow cellularity < 30%
- **TWO** of the following blood criteria:
    - neutrophils < 500/mm^3
    - platelets < 20,000/mm^3
    - absolute reticulocyte count < 40,000/mm^3

Allogeneic HSCT for Aplastic Anemia: Allogeneic hematopoietic stem-cell transplantation (HSCT) is a standard treatment option for individuals with severe AA. Allogeneic HSCT from a human leukocyte antigen (HLA)-matched sibling donor provides curative therapy for individuals with severe AA. It is considered a standard of care for individuals younger than 45 o 50 years of age, despite treatment-related morbidity and mortality (Young, 2008).

Hematopoietic recovery is often incomplete after immunosuppressive treatment, but tends to be complete and stable after HSCT (Young, 2008). The probability of survival with sustained donor engraftment for individuals with severe AA undergoing allogeneic HSCT is >80%, with younger patients having even better outcomes (Velardi, 2007). In children, matched-sibling-donor allogeneic HSCT has a >90% five-year overall survival (OS) rate (Bakhshi S., 2011), with ten-year outcomes of 97% reported for some children (Davies, 2007).

Young adults have a reasonable opportunity for cure with bone marrow transplantation but also face more complications than children (Young, 2006). Older individuals and those without HLA-identical related donors generally receive first-line therapy with immunosuppressive drugs. Alternative donor transplantation may be an option in children who do not have an HLA-matched donor. Disadvantages to allogeneic HSCT are procedure-related morbidity and mortality, especially graft-versus-host disease (GVHD) in older patients, and an increased incidence of solid organ malignancies (Young, 2005; Ades, et al., 2004). Graft failure after HSCT remains a significant problem in patients with AA, especially in those patients who have been heavily transfused (Champlin, 2007).

Literature Review
Although data from randomized controlled trials (RCTs) are lacking, a large number of case series and retrospective analyses report improved outcomes with the use of allogeneic HSCT.

Peinemann et al. (2013) reported results of a Cochrane systematic review with the primary outcome of evaluating the effectiveness and adverse events of first-line allogeneic hematopoietic stem cell transplantation of HLA-matched sibling donors compared to first-line immunosuppressive therapy in patients with acquired severe aplastic anemia. Three prospective trials involving 302 patients were included in the review. No trial was a randomized clinical trial. The authors reported that all studies had a high risk of bias due to the study design. The pooled hazard ratio for overall mortality for the transplant group versus the immunosuppressive therapy group was 0.95 ($p = 0.90$, low quality evidence). Overall mortality was not statistically significantly different between the groups. Treatment-related mortality ranged from 20% to 42% for the transplant group and was not reported for the immunosuppressive therapy group (very low quality evidence). Graft failure was 3%-16% for the transplant group and GVHD was from 26%-51%. Neither endpoint was applicable for the immunosuppressive therapy group. No data was reported by individual study authors regarding response and relapse for the transplant group. None of the included studies addressed health-related quality of life. The percentage of the evaluated patients with a Karnofsky performance status score in the range of 71% to 100% was 92% in the transplant group and 46% in the immunosuppressive therapy group. All studies were conducted more than 10 years ago; Cochrane authors note that these results may not be applicable to the standard of care of today. Due to limited, low quality data, with a high risk of bias, there are insufficient evidence to draw conclusions regarding the comparative effectiveness of first-line allogeneic HSCT with an HLA-matched sibling donor compared with first-line immunosuppressive therapy.

Pienemann et al. (2011) published a meta-analysis of 26 studies comparing results achieved by use of a matched related donor HSCT compared with immunosuppression (IST) as first-line therapy. No randomized clinical trial was identified. A systematic review was performed on overall survival. On multivariate analysis, younger age was identified as a statistically significant factor for improved survival in individuals who received HSCT. Overall mortality was reported in 23 studies (HSCT vs. IST: 3%–67% vs. 9%–58%, respectively).

In several recent studies OS rates are 51% to 100% for a range of time intervals (Perez-Albuerne, 2008; Inamoto, 2007; Unal, 2007). In a prospective study of individuals who were treated with allogeneic HSCT after failure with immunosuppressive therapy compared with those who received only immunosuppression, four-year failure-free survival, defined as survival with response, was 83.9% in the transplantation group compared with 9.1% in the group who received immunosuppressive therapy alone (Kosada, 2008).

The toxicity of myeloablative allogeneic HSCT has led to investigation of non-myeloablative conditioning and allogeneic HSCT for selected individuals who have failed previous immunosuppressive therapy and/or who are transfusion dependent. Data from RCT are lacking; however, several small case series and retrospective analyses report durable engraftment and four-year OS of 93% and 89%, respectively, for individuals receiving sibling-matched and unrelated donor allografts, and five-year OS rates of 84% (Kennedy-Nasser, 2006; Resnick, 2006).

Summary for Aplastic Anemia: Although data are not robust, allogeneic hematopoietic stem-cell transplantation (HSCT) is considered a standard of care treatment option for individuals with severe aplastic anemia.

Fanconi Anemia

Fanconi anemia (also called Fanconi's anemia, FA, and aplastic anemia with congenital anomalies) is a form of congenital aplastic anemia. It is a rare, genetic disorder of autosomal recessive inheritance, characterized by congenital abnormalities, progressive bone marrow failure, spontaneous and induced chromosome breakage and increased cancer susceptibility (Gluckman, 2007). At least thirteen genes have been implicated in the disease (Gluckman, 2007). Survival after diagnosis can range from two to 25 years. By age 40 to 48 years, the estimated cumulative incidence of bone marrow failure is 90%.

Allogeneic hematopoietic stem-cell transplantation (HSCT) can rescue aplastic anemia and prevent the occurrence of clonal hematopoietic disorders and is considered the treatment of choice for patients with severe hematological changes (Bonfim, 2007; Freedman, 2007; Velardi, 2007; Bitan, 2006; Motwani, 2005).

Literature Review

Allogeneic HSCT for Fanconi Anemia (FA): HSCT is currently the only curative therapy for the hematological abnormalities of FA. Although randomized controlled trials (RCT) data are lacking and evidence is not robust, FA is a universally accepted indication for allogeneic HSCT with a human leukocyte antigen (HLA)-identical sibling donor. FA is a rare disease, and, consequently, patient populations for many transplantation series have been comparatively small. Data from case series, retrospective analyses and review of registry data suggest improved long-term outcomes with allogeneic HSCT. In a retrospective review of one cohort of 43 individuals with FA, overall survival (OS) was 93% at 3.7 years (Bonfirm, 2007). In a retrospective analysis of 64 individuals who received allogeneic HSCT for FA overall eight-year event-free survival for the total population was 66%; eight-year OS was 67% (Locatelli, 2007). Farzin et al. (2007) reported 10-year OS rates of 89% in a cohort of 35 patients with FA who underwent allogeneic HSCT. Pooled published data on HSCT using HLA-matched sibling donors show a survival of greater than 80% in FA patients less than 10 years of age, and greater than 65% for FA patients of all ages (Freedman, 2008).

Alternative donors may be considered for individuals without other options; however, survival is generally less than with matched sibling donors (Guardiola, 2000). Graft-versus-host disease (GVHD) is more likely to be severe in patients with FA because of the underlying defect. However, outcomes were favorable compared with survival using matched related donors in a recent series of 12 consecutive children (Zecca, 2014). Participants had neither an HLA-identical sibling nor an HLA-matched unrelated donor and received haploidentical related donor reduced-intensity allogeneic HSCT. Cumulative incidences of grades II to IV acute and chronic graft-versus-host disease were 17% and 35%, respectively. The cumulative incidence of transplant-related mortality was 17%. The 5-year overall survival, event-free survival, and disease-free survival were 83%, 67%, and 83%, respectively.

Reduced-dose or non-myeloablative conditioning regimens may result in acceptable toxicity, high engraftment rates, improved survival and comparable incidences of GVHD compared with standard dose regimens utilized for hematological malignancies (Balci, 2008; Bonfirm, 2007; Bitan, 2006; Tan, 2006; Yabe, 2006; Janis-Netro, 2005). Data are not robust, and patient populations are small; nonetheless, this therapy may allow allogeneic transplantation in patients who are older, have co-morbid conditions, or have toxicities from previous treatment. Patients with minimal and chemotherapy-sensitive disease transplanted early in their disease course may have better outcomes.

Summary for Fanconi Anemia: Although randomized control trial data are lacking, allogeneic HSCT is considered a standard of care treatment option for individuals with Fanconi anemia.

Professional Societies/Organizations

National Marrow Donor Program (NMDP): The NMDP lists severe aplastic anemia and other bone marrow failure states including Fanconi anemia as indications for HSCT.

Use Outside of the US

British Committee for Standards in Hematology (BCSH) General Hematology Task Force (2009): On behalf of the BCSH, Marsh et al. (2009) published guidelines recommending allogeneic hematopoietic stem-cell transplantation (HSCT) as the initial treatment of choice for newly diagnosed patients with very severe or severe aplastic anemia, and a human leukocyte antigen (HLA)-compatible sibling donor. Immunosuppressive therapy is recommended for patients with non-severe aplastic anemia who are transfusion dependent, patients with severe or very severe disease who are >40 years old, and younger patients with severe or very severe disease who do not have an HLA-identical sibling donor. Matched unrelated donor bone marrow transplant may be considered

when a patient has severe aplastic anemia, has no matched sibling donor but a matched unrelated donor, is <50 years old (or 50–60 years old with good performance status), and has failed at least one course of ATG and cyclosporine.

Summary
Although data are not robust, the published, peer-reviewed evidence supports the safety and effectiveness of allogeneic hematopoietic stem-cell transplantation (HSCT) for this indication. Additionally allogeneic HSCT is considered a standard of care treatment option for an individual with severe aplastic anemia or Fanconi anemia.

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 when used to report allogeneic bone marrow or blood-derived stem cell procedures:

CPT®* Codes	Description
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
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
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
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation, per donor
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 of pre-and post-transplant care in the global definition

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