



CIGNA MEDICAL COVERAGE POLICY

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Subject Stem-Cell Transplant for Chronic Myelomonocytic Leukemia (CMML) and Juvenile Myelomonocytic Leukemia (JMML)

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- Donor Leukocyte Infusions
- Stem-Cell Transplant for Myelodysplastic Syndrome
- Transplant Donor Charges
- Umbilical Cord Blood Banking

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Coverage Policy

CIGNA covers myeloablative allogeneic hematopoietic stem-cell transplantation (HSCT) as medically necessary for the treatment of chronic myelomonocytic leukemia (CMML) and juvenile myelomonocytic leukemia (JMML) when a human leukocyte antigen (HLA) matched donor (at least five of six match) is available.

CIGNA covers non-myeloablative allogeneic HSCT as medically necessary for the treatment of CMML and JMML when the individual is not a candidate for myeloablative allogeneic HSCT and an HLA-matched donor (at least five of six match) is available.

CIGNA does not cover autologous HSCT for the treatment of CMML or JMML because it is considered experimental, investigational or unproven.

General Background

Chronic myelomonocytic leukemia (CMML) and juvenile myelomonocytic leukemia (JMML) are clonal myeloid disorders with both dysplastic and proliferative features, and are classified by the World Health Organization as Myelodysplastic/Myeloproliferative Diseases (MDS/MPD) (National Cancer Institute [NCI], 2008).

The median age of CMML is 65 to 75 years (NCI, 2008). Up to 75% of patients are over age 60 at the time of diagnosis. According to the NCI (2008), CMML is characterized pathologically by:

- persistent monocytosis $>1 \times 10^9/L$ in the peripheral blood
- no Philadelphia chromosome or BCR/ABL fusion gene
- $<20\%$ blasts in the blood or bone marrow
- dysplasia involving one or more myeloid lineages, or, if myelodysplasia is absent or minimal and all other causes have been ruled out, either an acquired clonal cytogenetic bone-marrow abnormality or at least three months of persistent peripheral-blood monocytosis, if all other causes are ruled out

Some cases may possess the gene translocation PDGFR-b-TEL. Symptoms may include weakness, infection, abnormal bleeding, and enlargement of the liver and spleen. According to Onida et al. (2002), poor prognosis is associated with the following factors:

- low hemoglobin level
- low platelet count with high white blood cell, monocyte and lymphocyte counts
- presence of circulating, immature myeloid cells
- high percentage of marrow blasts
- low percentage of marrow erythroid cells
- abnormal cytogenetics
- high levels of serum lactate dehydrogenase (LDH) and beta2-microglobulin

Median survival ranges from 12–24 months, with a progression to acute leukemia in 15%–20% of cases (NCI, 2008).

JMML is a rare hematologic malignancy accounting for two percent of all childhood leukemias (NCI, 2008). The cause of JMML is not known. The median age of presentation for JMML is under the age of one year. According to the NCI (2006), JMML is defined by:

- lack of the Philadelphia chromosome or BCR/ABL fusion gene
- peripheral-blood monocytosis $>1 \times 10^9/L$
- $<20\%$ blasts (including promonocytes) in the blood and bone marrow.

Two of the following four criteria are also required for diagnosis:

- increased fetal hemoglobin (Hb F) level for age
- immature granulocytes in the peripheral blood
- white blood cell count $>1 \times 10^9/L$
- clonal chromosomal abnormality, such as monosomy 7
- granulocyte-macrophage colony-stimulating factor (GM-CSF) hypersensitivity of myeloid progenitors in vitro

The symptoms of JMML include lethargy, pallor, fever, symptoms of bronchitis or tonsillitis, abnormal bleeding and bruising, maculopapular skin rashes, and enlargement of the liver, spleen, and lymph nodes. JMML has a poor prognosis and is resistant to chemotherapy. The median survival time 10 months to four years; prognosis is related to the age at diagnosis (NCI, 2008). Children $<$ one year of age at diagnosis have a better prognosis than children $>$ two years.

Treatment

CMML: Stem-cell transplantation is the only therapy that offers a chance for cure in CMML. Allogeneic stem-cell transplant can be considered in younger, healthy patients with appropriate donor matches. Various chemotherapy regimens, including topotecan, topotecan with cytarabine, and hydroxyurea, have been used with only modest success. Responses achieved are usually of short duration (NCI, 2008).

JMML: No therapy is consistently effective for JMML. Historically, over 90% of patients have died despite the use of chemotherapy (NCI, 2008). Allogeneic stem-cell transplantation is the only curative approach for JMML resulting in overall survival in more than half of the patients (Hasle, 2007). Research is currently underway to

evaluate the use of farnesyltransferase inhibitors, which may result in inhibition of tumor-cell growth and increased tumor cell apoptosis (NCI, 2006).

Stem-Cell Transplant

Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSCs) into a patient. HSCs are immature cells that can develop into any of the three types of blood cells (red cells, white cells or platelets). HSCs are created in the bone marrow and are found in the bone marrow and peripheral blood. There is also a high concentration of HSCs in umbilical-cord blood. HSC transplantation (HSCT) can be either autologous (i.e., using the patient's own stem cells) or allogeneic (i.e., using stem cells from a donor). HSCT is provided to patients with hematological malignancies to rescue them from treatment-induced aplasia, after high-dose chemotherapy and/or radiotherapy has been administered to eliminate the cancer.

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. Individuals under consideration for hematopoietic cell transplantation require an extensive evaluation performed by a transplant physician. A comprehensive pre-transplant evaluation will do the following (National Marrow Donor Program [NMDP], 2006):

- determine the patient's health and performance status
- determine the patient's disease status
- guide the informed consent process
- identify any psychiatric and/or social behaviors that may exclude the patient

Contraindications

There are many reasons that individuals fail treatment with HSCT, including graft failure, relapse of disease and side effects of treatment. Treatment-related deaths are due to infections, regimen-related toxicity and GVHD.

The presence of any significant comorbid conditions which would significantly compromise clinical care and chances of survival is a contraindication to transplant. Advanced age in the setting of myeloablative chemotherapy may limit survival; greater age is associated with a higher incidence of post-transplantation complications. Some chemotherapy agents used in the transplant conditioning regimen can reduce diffusion capacity; pulmonary complications are a significant cause of post-transplant morbidity and mortality. Additionally, a reduced ejection fraction and a history of congestive heart failure are associated with cardiotoxicity following transplant. The potential for exposure to nephrotoxic agents following transplant makes adequate renal function a necessity. 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), unless related to acute myelogenous leukemia
- poor renal function (creatinine clearance less than 50 mL/min)
- poor pulmonary function (diffusion capacity 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 2**

** EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE SCALE AND CORRESPONDING KARNOFSKY RATING

ECOG-PS GRADE	DESCRIPTION	KARNOFSKY RATING
0	Fully active, able to carry on all pre-disease activities without restriction	100
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)	80–90

**** EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE SCALE AND CORRESPONDING KARNOFSKY RATING**

ECOG-PS GRADE	DESCRIPTION	KARNOFSKY RATING
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours	60-70
3	Capable of only limited self-care; confined to bed or chair 50% or more of waking hours	40-50
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair	30 or less

(Niederhuber, 2000)

Myeloablative Allogeneic Transplant: In allogeneic HSCT, HSCs are grafted from a donor into a recipient. For an allogeneic HSCT to be successful, the donated cells must be similar, or a match, to the recipient's. Human leukocyte antigen (HLA) typing can identify donors who may be perfect matches. HLAs are proteins on a cell's surface that help the immune system identify the cell as either belonging to or from outside the body. There are three types each of class I and class II HLA. Increased survival is associated with a match between recipient and donor HLA-A, HLA-B, HLA-C, HLA-DRB1 and HLA-DQB1 (Morishima, et al., 2002).

For any given patient, there is a 25% chance that a sibling is an HLA-identical match. A sibling who has a class I and class II HLA match is called a related donor. An identical twin is termed a syngeneic match. For a patient who does not have a matched, related donor, a search for someone with matching HLA types is initiated through donor banks. In most cases, a matched, unrelated donor (MUD) can be found by searching the National Marrow Donor Program (NMDP). If no MUD can be located, a partially-matched (i.e., haploidentical) family member can donate stem cells. Unrelated donors, unrelated umbilical-cord blood donors and partially-matched family donors are all categorized as alternate stem-cell donors. Historically, outcomes after transplantation from unrelated donors have been poorer than those after matched-sibling donor transplantation, primarily because of increased rates of graft rejection and graft-versus-host disease (GVHD). Depletion of T cells from the transplant is associated with a significantly lower incidence of both acute and chronic GVHD, but also may result in an increased incidence of relapse (Bhushan and Collins, 2003).

Conditioning (i.e., ablative) regimens prepare the recipient for HSCT by eliminating any remaining recipient stem cells, suppressing the host immunity, and creating space to facilitate engraftment of donor stem cells. Pediatric myeloablative regimens have replaced radiation with busulfan to decrease the incidence of long-term adverse effects.

According to the NCI (2008) bone marrow or stem cell transplantation appears to be the only current treatment that alters the natural history of CMML. Additionally, allogeneic HSCT offers the best chance of cure for JMML (Niemeyer, et al., 1997; NCI, 2008). A recent report from the European working group on myelodysplastic syndrome in Childhood (EWOG-MDS) by Yoshima indicates an event-free survival of 52% at five years. Relapse remains the major cause of treatment failure, affecting about one-third of the patients following transplantation. A second allogeneic HSCT after relapse has been proposed but data on the possibility of a cure with this treatment are not available (Yoshima, 2007).

Non-Myeloablative Transplant: Non-myeloablative preparative regimens (also called mini-transplants) are designed to reduce regimen-related toxicities and allow allogeneic HSCT in patients who are older, have comorbid conditions or have toxicities from previous treatment (Maloney, et al., 2002). Non-myeloablative conditioning regimens fall into two categories: reduced intensity and minimally myelosuppressive. The conditioning regimens vary by study protocol and may include a purine analog, an alkylating agent, or low-dose, total-body irradiation. The purine analogs (including fludarabine, cladribine, and pentostatin) are broadly cytotoxic, as well as immunosuppressive.

The reduced-intensity, non-myeloablative preparative regimen relies on cytotoxic conditioning to maintain an anti-tumor effect and eliminate GVHD. The recipient becomes aplastic before engrafting donor cells. This

regimen retains the toxic side effects of high-dose treatments, although to a lesser degree. The reduced-intensity strategy is more likely to be tried in rapidly progressive diseases, in which a certain amount of cytoreduction is necessary to minimize residual disease, and the graft-versus-leukemia effect is less potent.

The minimally-myelosuppressive regimen uses immunosuppression before and after transplant to reduce GVHD and allow donor engraftment. This strategy employs the graft-versus-leukemia effect to eradicate the malignant recipient cells. Recipient cells are not completely eliminated by the conditioning regimen; therefore, a state of mixed chimerism (defined as the concurrent presence of donor and recipient hematopoietic cells) is created. Eventually, the immune response of the donor cells eradicates any remaining malignant recipient cells. The minimally-myelosuppressive regimen is more likely to be tried in diseases such as low-grade lymphoma and chronic leukemia, where immunosuppression alone is likely to permit engraftment, and the graft-versus-leukemia effect is greater.

Non-myeloablative allogeneic HSCT is a feasible option for patients with MDS for whom fully ablative dose chemotherapy followed by allogeneic HSCT is not appropriate; likewise, this therapy may result in improved outcomes for patients with CMML and JMML, as these disorders share dysplastic characteristics.

Autologous Transplant: In autologous HSCT, the recipient's own previously harvested stem cells are reinfused. Autologous HSCT may provide an alternative stem-cell source for patients who do not have HLA-matched donors. It can also be performed in older patients, since the conditioning regimen for autologous HSCT is less toxic than the one for allogeneic HSCT and does not create a graft-versus-host reaction. This lack of graft-versus-leukemia reaction, however, results in greater chances of disease relapse with autologous HSCT than with allogeneic HSCT. Contamination of autografts by malignant cells may account for the difference.

There is a paucity of data regarding autologous HSCT for the treatment of CMML and JMML. Overall, the published peer-reviewed medical literature contains insufficient evidence to support the use of autologous HSCT for the treatment of CMML or JMML.

Source of Cells

HSCs are available in the peripheral blood, bone marrow, and umbilical cord.

Peripheral-Blood Stem-Cell (PBSC) Transplant: Stem cells are present in the peripheral blood but in such small numbers that ordinary blood tests cannot identify them. There is, however, a medication (i.e., filgrastim) that the donor can take to induce stem cells to leave the marrow and enter the blood, where they can be collected (i.e., harvested). Mobilizing stem cells allows collection of significantly more stem cells than could be harvested from bone marrow. Several studies have demonstrated faster neutrophil and platelet engraftment, reduced early toxicity, and superior immune reconstitution after allogeneic HSCT with PBSCs than with bone-marrow stem cells (Bensinger, et al., 2001; Hagglund, et al., 1998; Mifflin, et al., 1997; Ringden, et al., 1999). Most HSCTs use PBSCs, as opposed to other stem-cell sources because of the relative ease of PBSC donation and the success of PBSCs as the transplant cell source.

Currently, phase III studies are being conducted to evaluate the relative efficacy of PBSC transplantation versus that of bone-marrow transplant from HLA-compatible unrelated donors for treatment of hematological malignancies (NCI, 2005).

Bone-Marrow Transplant (BMT): Bone marrow is used for HSCT because it contains a relatively large number of HSCs. Bone marrow is removed from the top of the donor's hip bone. The bone marrow is then filtered, treated, and either transplanted immediately or frozen and stored for later use. When the recipient is ready for the transplant, the transplant material is transfused into the patient through an IV line into a vein and is naturally transported back into the bone cavities, where it grows to replace the recipient bone marrow. Because of the relative difficulty of the donation process and the increased risk to the donor from anesthesia, BMT is performed less commonly than PBSC transplantation.

Umbilical-Cord Blood Transplant (UCBT): Blood in the umbilical cord contains a high proportion of stem cells. The umbilical cord itself, however, yields only a small volume of blood. Therefore, a donation of stem cells from one umbilical cord yields fewer stem cells than a donation from bone marrow or from peripheral blood. This lower stem-cell yield limits the usefulness of UCBT in adults. The single most important factor influencing time to hematopoietic recovery in adults appears to be the nucleated-cell content of the graft relative to the recipient

size (Grewal, et al., 2003; Rubinstein, et al., 1998). Studies are being conducted to evaluate the feasibility of ex vivo expansion of UCB stem cells for use in adult or larger pediatric patients.

Potential advantages of UCBT over marrow or blood stem-cell transplants include (Barker, et al., 2001; Gluckman, et al., 1997; Hayes, 2005; Laughlin, et al., 2001; The Leukemia & Lymphoma Society, 2008):

- large potential donor pool
- rapid availability, since the cord blood has been prescreened, tested and frozen and is ready to use
- no donor attrition, since the UCB stem cells are already stored
- no risk or discomfort for the donor
- low incidence of contamination by viruses
- lower risk of GVHD, even for recipients with a less-than-perfect tissue match

Disadvantages of UCBT include:

- potential for diseases that have not developed in the donor to be transmitted to the recipient
- unclear long-term success
- slower engraftment rate, potentially leaving the recipient at risk for life-threatening infections

Literature Review

Myeloablative Allogeneic HSCT

CMML: Elliott et al. (2006) reviewed the results of 17 consecutive adult patients with CMML who underwent allogeneic HSCT from related (n=14) and unrelated (n=3) donors. Median age was 50 years. Seven patients demonstrated relapse or persistent disease at a median of six months. Six patients underwent donor lymphocyte infusions (DLI). Two patients achieved durable remissions of 15 months. Overall transplant-related mortality was 41%. With a median follow-up of 34.5 months, three patients (18%) remain alive and in complete remission (CR). The authors noted that a graft-versus-leukemia effect was demonstrated for both the transplant and DLI. They also noted that outcomes remain less than optimal.

Karrabul et al. (2005) evaluated the outcomes for 23 patients with CMML who underwent allogeneic HSCT. Patients ranged in age from 1–66. The transplant-related mortality rate was 34% and was primarily because of GVHD or multigrain failure. Median survival was 69 months. The estimated four-year overall and progression-free survival rates were 41%. Patients with fewer comorbidities and who underwent HSCT earlier in the disease process had better outcomes, although the small size of the study limits the power of the associations. While GVHD and treatment-related mortality remain a significant problem, this study demonstrates improved outcomes over historical data.

In the largest cohort study to date of adult patients with CMML Kroger et al. (2002) reviewed the results of 50 allogeneic transplant recipients. The five-year estimated overall survival was 21%. Those who experienced acute GVHD displayed a lower rate of relapse, while those with T-cell-depleted grafts experienced a higher relapse rate. The authors noted that this evidence supports a graft-versus-leukemia effect in allogeneic HSCT for CMML.

Arnold et al. (1998) conducted a review of 118 patients who received MUD transplants for various hematological malignancies. Twelve of the patients had CMML. Transplant-related mortality was high and increased with recipient age. Of the patients with CMML, actuarial survival at two years was only 10%. Many of these transplants were conducted prior to 1986, however, when patient selection criteria and HSCT techniques were still being developed.

Although disease relapse, TRM and GVHD remain significant issues associated with myeloablative allogeneic HSCT for CMML, this treatment option offers the best chance for cure for this disease.

JMML: Yoshima et al. (2007) reported the outcomes of second transplantation in 24 children with JMML relapsing after first allogeneic transplantation. Initially, 183 patients registered in the prospective and retrospective studies of EWOG-MDS underwent allogeneic HSCT. Sixty-eight patients relapsed and 26 patients received a second graft. Two patients were excluded due to insufficient data. The median age was 3.6 years. The median time from first to second transplantation was 260 days. The five-year cumulative incidence of treatment-related mortality (TRM) was 27%. The five-year cumulative incidence of relapse was 40%. The

probabilities for leukemia-free survival (LFS) at three and five years were 50% and 32%, respectively. The authors note that the results of a second transplant are superior to those achieved with DLI and similar to those of first HSCT; however, they also note that longer follow-up is needed to evaluate the long-term outcome of these patients.

Korthof et al. (2005) reviewed outcomes for 23 children who received allogeneic HSCT for JMML. At the time of the report, eleven patients were in full or partial remission (48%), eight relapsed (35%) and four died of transplant-related causes (17%). The estimated overall survival rate for this cohort was 43.5% at four years. The median follow-up of the nine patients in complete remission was six years. Factors related to outcomes were evaluated, but the small size of the study limits the power of these observations.

On behalf of the European Working Group on Myelodysplastic Syndrome in Childhood, Locatelli et al. (2005) reported the outcomes of 100 children with JMML (67 boys and 33 girls) who received allogeneic HSCT between 1993 and 2002. The transplants were performed at 29 centers in seven countries. Data was collected by standardized questionnaires. The median age at presentation was 1.4 years. Forty-eight children received the allograft from an HLA-identical relative; 52 children received a matched-unrelated allograft. To evaluate the impact of therapy received before transplantation on the outcomes post-transplantation, patients were divided into two groups. Group one children (n=84) were given either no chemotherapy before transplantation, differentiative therapy (i.e., cis-retinoic acid) or low-intensity therapy. Group two children (n=16) had received therapy similar to that given children with acute myeloid leukemia. Grades II–IV acute GVHD developed in 40 patients. Five-year cumulative incidence of transplant-related mortality was 13%. The median time to treatment-related death was 2.7 months. The five-year Kaplan-Meier estimate of survival is 64%. The five-year probability of event-free survival (EFS) after the first allograft is 52%. Univariate analysis of factors related to the patient, disease and transplantation influencing EFS showed that male sex and both age at diagnosis and age at transplantation being younger than four years were associated with a better outcome. Prior therapy was not shown to have an impact on EFS, risk of relapse or transplant-related mortality. The authors noted that this study confirms the conclusion of previously published studies that relapse is the major cause of treatment failure. The authors also noted that HSCT, after a preparative regimen of busulfan, cyclophosphamide and melphalan, may cure approximately 50% of patients with JMML. While disease relapse remains a significant issue, these outcomes support the efficacy of allogeneic HSCT for the treatment of JMML.

In a prospective trial by the Children's Cancer Group reported by Woods et al. (2002), 90 children with JMML, acute myelogenous leukemia or MDS were treated with an induction regimen and then allocated to allogeneic BMT if matched, related donors were available. Patients without appropriate donors were randomized between autologous BMT and aggressive non-myeloablative chemotherapy. Patients with JMML experienced overall remission rates of 58%. For patients achieving remission, long-term survivors were found among those receiving either allogeneic BMT or chemotherapy.

For JMML, the relative effectiveness of allogeneic HSCT from matched, related donors is supported by a retrospective analysis of 43 children who received BMT (Locatelli, et al., 1997). Patients with matched, related donors experienced significantly less treatment-related mortality (9%) than did those with MUDs (46%). The total population experienced a five-year event-free survival of 31%.

Arico et al. (1997) reviewed 16 different studies covering a total of 91 patients with JMML who were treated with bone-marrow transplantation (BMT). Patients receiving transplantation of matched, related donor HSCs survived significantly longer than did patients treated with chemotherapy.

Non-myeloablative Allogeneic HSCT

Laporte et al. (2008) reported the outcomes of 148 patients with de novo MDS (n=40), acute myelogenous leukemia after antecedent MDS/MPD (n=49), treatment-related MDS (n=25), MPD (n=27) and CMML (n=7) who underwent allogeneic HSCT using reduced or nonmyeloablative conditioning prior to transplantation. Transplantations took place at 14 institutions. The primary differences between conditioning protocols were the use of HLA-matched related or unrelated grafts, duration and intensity of chemotherapeutic agents and the addition of fludarabine to total body irradiation. The median patient age was 59. At a median follow-up of 47 months, the three-year relapse-free and overall survival was 27% and 27% for all patients. Relapse-free and overall survival rates at three years for patients with CMML were 43% and 43%. The authors note that nonmyeloablative allogeneic HSCT confers remissions in patients were otherwise not eligible for HSCT but for

whom relapse is the leading cause of treatment failure. The authors also note that further investigation is warranted to determine the optimal regimen with adequate dose intensity and low toxicity.

Nakamura et al. (2007) retrospectively evaluated the outcomes of 28 patients with MDS and 15 patients with acute myeloid leukemia (AML) arising from prior MDS who underwent a reduced-intensity conditioning (RIC) allogeneic transplant using an HLA-identical sibling or unrelated donor. According to the International Prognostic Scoring System (IPSS), two patients had low, ten had intermediate-1, nine had intermediate-2 and seven had high-risk MDS. Cytogenetic features were considered high-risk in 19, intermediate-risk in 17 and good-risk in seven patients. The median ages of patients with a sibling donor or unrelated donor were 59 years and 52.5 years, respectively. Eleven patients had undergone a previous autologous HSCT. At the time of transplant, 79% of the patients had persistent MDS (n=27) or AML (n=7). Following transplant, 89% of these patients had no evidence of disease by day +30 by bone marrow morphology and cytogenetics/FISH. One-hundred day TRM was 27.4%, while two-year TRM was 35.2%. The two-year overall survival (OS), disease-free survival (DFS) and relapse rates were 53.5%, 51.2%, and 16.3%, respectively. There was no significant difference in OS or DFS IPSS/disease status or cytogenetics. The authors note that a low relapse rate after a relatively long follow-up period in this case series suggests that a graft-versus-leukemia (GVL) effect can be expected in the RIC-HSCT setting.

Martino et al. (2006) retrospectively analyzed the outcomes of 836 patients with MDS who underwent allogeneic HSCT with an HLA-identical sibling donor. Six hundred twenty-one patients received myeloablative conditioning, and 215 patients received RIC. In multivariate analysis, the three-year relapse rate was significantly increased after RIC (hazard ratio [HR] 1.64; p=0.001), but the three-year nonrelapse mortality rate was decreased in the RIC group (HR 0.61; p=0.015). The three-year probabilities of progression-free and overall survival in myeloablative and RIC were similar in both groups (39% versus 33% and 45% versus 41%, respectively). The authors noted that these results are encouraging; however, based on the higher risk of relapse with RIC, patients should not receive this treatment outside of prospective randomized trials. These trials are needed to establish the position of RIC-based HCT in the treatment of patients with MDS.

Alyea et al. (2006) retrospectively reviewed the results of 136 patients with advanced AML and MDS undergoing allogeneic HSCT. Thirty-nine patients received RIC and allogeneic HSCT compared to 97 patients who received myeloablative conditioning and HSCT. Of the patients with MDS, 16 received RIC, while 38 patients received myeloablative conditioning. All patients receiving RIC were evaluated for myeloablative conditioning and determined to be ineligible for that procedure. Patients receiving RIC were at high risk for complications, as they were older (57 versus 43 years, p=0.001) and more likely to have received previous HSCT (54% versus 2%, p=.0001). The incidence of grade II-IV acute GVHD was similar in patients receiving RIC compared to those receiving myeloablative conditioning: 26% and 27%, respectively. No significant difference in two-year OS was seen in patients receiving RIC and those who received myeloablative transplant, 28% and 34%, respectively. Likewise, no significant difference was noted in two-year progression-free survival (PFS) for patients receiving RIC or myeloablative transplantation, 20% and 31%, respectively. Cox regression analysis identified no factors, including the intensity of the conditioning regimen, which influenced either OS or PFS. The authors noted that this study suggests the less toxic non-myeloablative regimen used produced results similar to those seen with myeloablative conditioning.

Koyama et al. (2005) report the results of a single pediatric patient of three years with JMML who received standard dose chemotherapy with cytarabine, etoposide and mitoxantrone with good response. Subsequently, she underwent an HLA-matched related allogeneic HSCT using reduced-intensity conditioning. She has maintained a CR and full donor chimerism at nine months after HSCT. The authors conclude that patients with JMML who respond to chemotherapy should be considered as candidates for reduced-intensity allogeneic HSCT.

There is evidence that the non-myeloablative approach to stem-cell transplantation is effective in patients with MDS who have failed conventional HSCT. Niederwieser et al. (2003) utilized an RIC protocol with low-dose, total-body irradiation and fludarabine prior to HSCT from unrelated donors in treating 52 patients. These patients had a variety of hematological diseases and either had high-risk features or had previously failed HSCT. At 19 months, the overall survival rate was 35%. Chakraverty et al. (2002) studied outcomes of 47 patients receiving reduced-intensity conditioning, with 29 of the patients having previously failed HSCT. Overall, progression-free survival rates were 75.5% at one year.

Maris et al. (2003) developed a non-myeloablative conditioning regimen followed by allogeneic HSCT for 89 patients with hematological malignancies, including those with MDS (n=21) and MPD (n=7). Patients with MDS/MPD were classified as having high-risk disease. All patients were not considered candidates for conventional high-dose HSCT because of age and/or other known risk factors, including previous failed allogeneic or autologous HSCT. The median age was 53 years. The probability of overall survival (OS) at one year was 52%; OS for patients with MDS/MPD was 29%. One-year overall progression-free survival (PFS) was 38%; for patients with MDS/MPD PFS, it was 25%. Disease responses were seen among all disease categories. The presence of active or chronic GVHD has been associated with a decreased risk of relapse.

Taussig et al. (2003) evaluated the use of RIC with allogeneic HSCT from HLA-identical family donors in 16 patients with MDS (n=6) or acute myeloid leukemia (AML) (n=10). The median age was 54 years. The authors did not report results separately for each diagnosis. There was no transplant-related mortality within 100 days of transplant. Acute GVHD occurred in three patients; chronic GVHD developed in 10 patients. Two-year actuarial overall and event-free survival rates were 69% and 56%, respectively. The authors noted that this therapy resulted in durable remissions. They also noted that evidence is accumulating that this treatment is relatively safe and effective and warrants further study.

Non-myeloablative preparative regimens followed by allogeneic HSCT have included recipients with various hematological conditions classified as MDS, including JMML and CMML. Several prospective case series have demonstrated the efficacy of this therapy in patients with high-risk MDS who are over age 50. Various reduced-intensity conditioning (RIC) regimens were utilized, including fludarabine and busulfan (Martino, et al., 2002; de Lima, et al., 2004), fludarabine, busulfan and alemtuzumab (Aloysius, et al., 2004), fludarabine and cyclophosphamide or melphalan (Taussig, et al., 2003) and CAMPATH-1H, fludarabine and melphalan (Chakraverty, et al., 2002). The event-free survival rates ranged from 56–73%, although the time intervals assessed were varied. The treatment resulted in low rates of severe GVHD and treatment-related mortality.

Autologous HSCT

Grainger et al. (2002) reported on a single case of JMML autografted from cultured HSCs. A chromosomal abnormality returned within five to seven months of the autograft, but the patient remained alive and in full cytogenetic remission 10 years after the procedure.

De Witte et al. (2001) investigated the use of unpurged, autologous autografts in patients with myelodysplastic syndromes and acute myeloid leukemia; patients with JMML or CMML were not specifically identified. The study included 19 MDS patients who had a two-year overall survival rate of 46%, a 5% treatment-related mortality rate, and a relapse rate of 69%. The authors attribute the high relapse to graft contamination.

Laporte et al. (1993) reported on seven patients with MDS in transformation to acute myeloblastic leukemia. One of the patients had CMML. Each of the patient's bone marrow was purged with mafosfamide prior to HSCT. One patient died from transplant-related toxicity; four relapsed up to 25 months after transplant; and two were in complete remission up to 28 months after remission. The authors suggest that transplanting bone marrow HSCs that have been purged with mafosfamide may be a feasible treatment, but this procedure must be evaluated in additional studies.

Professional Societies/Organizations

The NCI (2008) notes bone marrow/stem cell transplantation appears to be the only current treatment that alters the natural history of CMML. Regarding JMML the NCI (2008) notes that no consistently effective therapy is available for JMML. Bone marrow transplantation seems to offer the best chance for a cure.

The National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology for Myelodysplastic Syndromes (2007) note that patients with MDS are classified as having one of five subtypes of disease which includes CMML. The Guidelines note that allogeneic HSCT from an HLA-matched sibling donor is a preferred approach for treating a portion of patients with MDS, particularly those with high-risk disease. For patients with an International Prognostic Scoring System (IPSS) Intermediate-2/High score, standard conditioning is used for relatively younger patients. The experimental approach using non-myeloablative conditioning is preferable in older individuals; the Guidelines recommend that these treatments be given in the context of clinical trials.

The American Cancer Society (2006) notes that stem cell transplant is the only treatment that can cure some patients with MDS/MPD.

The Leukemia & Lymphoma Society (2004) notes that improvement in survival does occur after stem cell transplantation from a compatible sibling for patients with JMML but a cure is uncommon. Regarding stem cell transplantation for CMML, the Society notes that stem cell transplantation can be considered in younger patients (i.e., <50 years) with a matched donor.

Summary

Chronic myelomonocytic leukemia (CMML) and juvenile myelomonocytic leukemia (JMML) are categorized as myelodysplastic/myeloproliferative diseases (MDS/MPD), as they have features of both disorders. Data suggest that the highest rates of cure for these diseases result from treatment with myeloablative allogeneic hematopoietic stem-cell transplantation (HSCT), although treatment-related mortality and disease relapse remain significant hurdles to the success of this procedure. The use of reduced-intensity or non-myeloablative conditioning regimens may enable patients who are unable to tolerate high-dose chemotherapy to undergo allogeneic HSCT. The published, peer-reviewed, scientific literature supports this therapy as a treatment for CMML and JMML. There is insufficient published, peer-reviewed scientific evidence to support the use of autologous HSCT in the treatment of CMML and JMML and, therefore, it remains experimental, investigational and unproven.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

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
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
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
38240	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic
38242	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor 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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†Note: Covered when medically necessary and when used to report allogeneic bone-marrow or blood-derived stem cell procedures.

ICD-9-CM Diagnosis Codes	Description
205.10	Chronic myeloid leukemia without mention of remission
205.11	Chronic myeloid leukemia in remission

Experimental/Investigational/Unproven/Not Covered:

CPT* Codes	Description
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38241	Bone marrow or blood-derived peripheral stem cell transplantation; autologous

***Current Procedural Terminology (CPT®) ©2007 American Medical Association: Chicago, IL.**

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Policy History

<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare	11/15/2008	0243	Stem-Cell Transplant for Chronic Myelomonocytic Leukemia (CMML) and Juvenile Myelomonocytic Leukemia (JMML)

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.