Aetna considers allogeneic (ablative and non-myeloablative) hematopoietic cell transplantation medically necessary for individuals with myelofibrosis (MF) when any of the following criteria is met:

- The individual is dependent on transfusions of red blood cells;
- The individual is dependent on transfusions of platelets or has frequent infarctions; or
- The individual has an absolute neutrophil count less than 1000/mm$^3$; or
- The individual is resistant to conservative therapy; or
- The individual has intermediate or high risk MF

Aetna considers a repeat allogeneic (ablative or non-myeloablative) hematopoietic cell transplantation medically necessary for individuals with myelofibrosis and primary graft failure or who have relapsed.

Aetna considers autologous hematopoietic cell transplantation experimental and investigational for myelofibrosis due to insufficient evidence in the peer-reviewed literature.

See also:

- CPB 0496 - Hematopoietic Cell Transplantation for Selected Childhood Solid Tumors,
- CPB 0507 - Hematopoietic Cell Transplantation for Breast Cancer,
- CPB 0617 - Hematopoietic Cell Transplantation for Testicular Cancer,
Background

Primary MF is considered a chronic myeloproliferative disorder and is characterized by variable degrees of cytopenia, cytosis, bone marrow fibrosis, a leukoerythroblastic blood picture, and extramedullary hematopoiesis, which can result in hepatosplenomegaly (Cervantes et al, 2009). MF is a heterogeneous disease in that MF is an indolent disease in some patients, who may survive for decades, to an aggressive disease in others, with disabling symptoms, lowered quality of life and in some cases survival of less than a year (McLornan et al, 2012). MF can be either primary or secondary, and can develop in patients with polycythemia vera or essential thrombocythemia. The median age is in the seventh decade and approximately 70% of patients are positive for the Janus2 kinase mutation (Ballen, 2012).

There have been no available conventional drug therapies for MF which have been shown to prolong survival. Palliative agents include erythropoietin, androgens, immunomodulatory agents, interferons, cytoreductive therapies and non-pharmacologic approaches. The non-pharmacologic approaches include blood transfusion, splenic irradiation, and splenectomy. Allogeneic hematopoietic stem cell transplantation (SCT) is considered to be the only potentially curative therapy for MF (McLornan et al, 2012).

The American Society for Blood and Marrow Transplantation Guideline on the role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of myelodysplastic syndrome states that” early SCT is recommended for patients with an International Prognostic Scoring System (IPSS) score of intermediate (INT) -2 (considered high risk) at diagnosis who have a suitable donor and meet the transplant 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) (Oliansky et al, 2009). The IPSS estimates survival from the time of diagnosis based on five risk factors: age > 65 years, hemoglobin < 100 g/l, leukocyte count > 25 x 10^9/l, circulating blasts ≥ 1%, and the presence of constitutional symptoms. Patients are then classified as low risk (score = 0), intermediate risk-1 (score = 1), intermediate risk-2 (score = 2), and high risk (score ≥ 2) (McLornan et al, 2012).

Cervantes et al (2009) studied 1054 patients at 7 centers who were diagnosed with primary MF. The purpose of this retrospective study was to develop a highly discriminative prognostic system. Variables selected for prognostic assessment...
were those previously shown to be of prognostic value in primary MF along with variables considered to be either clinically meaningful or potential confounders. Analysis using Cox proportional hazards modeling revealed identified age greater than 65 years, presence of constitutional symptoms, hemoglobin level less than 10 g/dL, leukocyte count greater than $25 \times 10^9$/L, and circulating blast cells 1% or greater as predictors of shortened survival. Overall median survival was 69 months (95% confidence interval: 61-71). Four risk groups with no overlap in their survival curves were identified, including 0 (low risk), 1 (intermediate risk-1), 2 (intermediate risk-2), or greater than or equal to 3 (high risk), with respective median survivals of 135, 95, 48, and 27 months ($p < 0.001$). Additionally, in 409 patients with assessable metaphases, cytogenetic abnormalities were associated with shorter survival, but their independent contribution to prognosis was restricted to patients in the intermediate-risk groups. JAK2V617F did not cluster with a specific risk group or affect survival.

A prospective multicenter trial was conducted in 103 patients with various forms of MF to determine the efficacy of a busulfan (10 mg/kg) fludarabine (180 based reduced-intensity conditioning regimen followed by allogeneic stem cell transplantation from related ($n = 33$) or unrelated donors ($n = 70$). Cumulative incidence of nonrelapse mortality at 1 year was 16% and was significantly lower for patients with a completely matched donor. The estimated 5-year event-free survival was 51% and 68%, respectively (Kroger et al, 2009).

Tefferi et al (2011a) noted that “current drug therapy in primary MF is neither curative or essential for survival. Similarly, it is not clear if the application of allogeneic SCT, with its attendant risk of death or chronic morbidity from graft-versus-host disease, has had a favorable or unfavorable net effect. Therefore, one must first determine whether a particular patient needs any form of therapy at all and, if so, carefully select the treatment strategy with the best chance of inducing disease control without compromising life expectancy.” Tefferi et al (2011b) reported that the presence of fibrosis, JAK2/MPL mutation or +9/13q- cytogenic abnormality is supportive but not essential for diagnosis, and that diagnosis is based on bone marrow morphology. The authors state that observation alone is adequate for asymptomatic low/intermediate-1 risk disease; allogeneic SCT or experimental drug therapy is reasonable for symptomatic intermediate-1 risk disease.

Alchalby et al (2012) evaluated 150 homogeneously treated MF patients who underwent reduced-intensity allogeneic SCT and developed a risk score for overall survival. The authors' prognostic scoring system compared to the Lille scoring system and correlated significantly with overall survival but discriminated poorly between the intermediate and high-risk groups. The authors concluded that a simple model which includes age, JAK2 V617F-status, and constitutional symptoms can clearly separate distinct risk groups. The authors further noted that such a model can be used in addition to the Lille model to predict overall survival after reduced-intensity allogeneic SCT.

Scott et al (2012) conducted a study to evaluate a Dynamic International Prognostic Scoring System (DIPSS) risk categorization. They evaluated the DIPSS in 170 MF patients aged 12 to 78 years who received SCT from related ($n = 86$) or unrelated ($n = 84$) donors. The investigators determined that 21 patients
had low-risk disease, 48 had intermediate-1, 50 had intermediate-2, and 51 had high-risk disease. Additionally, they reported five-year incidence of relapse, relapse-free survival, overall survival, and nonrelapse mortality for all patients were 10%, 57%, 57%, and 34%, respectively. They concluded that SCT was curative for a large proportion of patients with MF, and post-SCT success was dependent on pre-SCT DIPSS classification.

In a recent review of allogeneic stem cell transplantation for MF, McLornan et al (2012) concluded that transplant-eligible MF patients with intermediate-2 and high-risk disease should be considered for SCT. Additionally, patients with transfusion dependency or an unfavorable karyotype should also be considered for SCT. The authors suggested a myeloablative conditioned approach in those greater than 45 years of age, and acknowledged that some patients between 45 and 50 years of age with low HCT-CI scores may well also be suitable for a myeloablative conditioned SCT. They further suggested that a reduced-intensity conditioning regimen be considered for those over the age of 45 years and that patients older than 65 years should not be definitively excluded from potential SCT on age criteria alone, but rather that “a frank discussion with the patient regarding the association of older age and, in general, an adverse post-SCT outcome should occur in addition to a detailed risk assessment”.

An UpToDate review on “Prognosis and treatment of primary myelofibrosis” (Tefferi, 2013) provides the following recommendations:

For younger patients (i.e., age less than 45 years) at intermediate-2 or high risk according to the DIPSS [Dynamic International Prognostic Scoring System] Plus scoring system, we suggest that the patient be considered for hematopoietic cell transplantation (HCT) shortly after diagnosis (Grade 2B). We prefer conventional intensity conditioning for those less than 45 years of age and reduced-intensity conditioning for those 45 to 65 years of age.

For DIPSS Plus low-risk patients, who might live 10 to 15 years with supportive treatment alone, but might have a transplant-related mortality of at least 8 percent, the answer is not yet clear. Until further information is available, we suggest against the use of HCT for this group of patients (Grade 2C).

In an update on the diagnosis, risk-stratification, and management of primary myelofibrosis (PMF), Tefferi et al (2014a) stated that PMF is a myeloproliferative neoplasm characterized by stem cell-derived clonal myeloproliferation, abnormal cytokine expression, bone marrow fibrosis, anemia, splenomegaly, extra-medullary hematopoiesis (EMH), constitutional symptoms, cachexia, leukemic progression, and shortened survival. Diagnosis is based on bone marrow morphology. The presence of JAK2, CALR, or MPL mutation is supportive but not essential for diagnosis; approximately 90% of patients carry 1 of these mutations and 10% are "triple-negative". None of these mutations is specific to PMF and is also seen in essential thrombocythemia (ET). Pre-fibrotic PMF mimics ET in its presentation and the distinction, enabled by careful bone marrow morphological
examination, is prognostically relevant. Differential diagnosis also includes chronic myeloid leukemia, myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia. The Dynamic International Prognostic Scoring System-plus (DIPSS-plus) uses 8 predictors of inferior survival: age greater than 65 years, hemoglobin less than 10 g/dL, leukocytes greater than 25 × 10^9 /L, circulating blasts greater than or equal to 1 %, constitutional symptoms, red cell transfusion dependency, platelet count less than 100 × 10^9 /L, and unfavorable karyotype (i.e., complex karyotype or sole or 2 abnormalities that include +8, -7/7q-, i(17q), inv(3), -5/5q-, 12p-, or 11q23 rearrangement). The presence of 0, 1, “2 or 3”, and greater than or equal to 4 adverse factors defines low, intermediate-1, intermediate-2, and high-risk disease with median survivals of approximately 15.4, 6.5, 2.9, and 1.3 years, respectively. High risk disease is also defined by CALR(-)/ASXL1(+) mutational status. Observation alone is adequate for asymptomatic low/intermediate-1 risk disease, especially with CALR(+) /ASXL1(-) mutational status. Stem cell transplant is considered for DIPSS-plus high-risk disease or any risk disease with CALR(-)/ASXL1(+) mutational status. Investigational drug therapy is reasonable for symptomatic intermediate-1 or intermediate-2 risk disease. Splenectomy is considered for drug-refractory splenomegaly. Involved field radiotherapy is most useful for post-splenectomy hepatomegaly, non-hepatosplenic EMH, PMF-associated pulmonary hypertension, and extremity bone pain.

About 5–18% of patients with myelofibrosis with myeloid metaplasia (MMM) who undergo allogeneic myeloablative transplantation will relapse after three years (Tanvetyanon and Stiff, 2004). Relapse carries a high mortality: half of the patients will die within a year. Increased age, impaired performance status, and reduced organ reserve often hamper further attempt at myeloablative chemotherapy.

Klyuchnikov, et al. (2012) reported the results of a second HSCT as salvage therapy in myelofibrosis patients who have relapsed or experienced graft rejection. Thirty myelofibrosis patients (21 males, nine females) with relapse (n = 27) or graft-rejection (n = 3) after dose-reduced allografting underwent a salvage strategy including donor lymphocyte infusions (DLIs) and/or second allogeneic hematopoietic stem cell transplantation (HSCT). Twenty-six patients received a median number of three (range, 1-5) DLIs in a dose-escalated mode starting with a median dose of 1·2 × 10^6 (range, 0·003-8 × 10^6 ) up to median dose of 40 × 10^6 T-cells/kg (range, 10-130 × 10^6 ). 10/26 patients (39%) achieved complete response (CR) to DLIs. Acute (grade II-IV) and chronic graft-versus-host (GvHD) disease occurred in 12% and 36% cases. Thirteen non-responders to DLI and four patients who did not receive DLI due to graft-rejection or acute transformation of the blast phase underwent a second allogeneic HSCT from alternative (n = 15) or the same (n = 2) donor. One patient (6%) experienced primary graft-failure and died. Acute (II-IV) and chronic GvHD were observed in 47% and 46% of patients. Overall responses after second HSCT were seen in 12/15 patients (80%; CR: n = 9, partial response: n = 3). The 1-year cumulative incidence of non-relapse mortality for recipients of a second allograft was 6%, and the cumulative incidence of relapse was 24%. After a median follow-up of 27 months, the 2-year overall survival and progression-free survival for all 30 patients was 70% and 67%, respectively. The investigators concluded that their two-step strategy, including DLI and second HSCT for non-responding or ineligible patients, is an effective and
well-tolerated salvage approach for patients relapsing after reduced-intensity allograft after myelofibrosis.

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes covered if selection criteria are met:

38204 - Bone marrow or stem cell services/procedures-allogenic
38205, 38207
- 38215,
38230, 38240,
38242

CPT codes not covered for indications listed in the CPB:

38232 Bone marrow harvesting for transplantation; autologous
38241 Bone marrow or blood-derived peripheral stem cell transplantation; autologous

ICD-9 codes covered if selection criteria are met:

289.83 Myelofibrosis

The above policy is based on the following references:


12. Tefferi A. Prognosis and treatment of primary myelofibrosis. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed September 2013.


