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AETNA BETTER HEALTH®

Clinical Policy Bulletin: Hematopoietic Cell Transplantation for Myelofibrosis

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Policy

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 transfusion dependent; 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 failure to engraft.

Aetna considers a repeat allogeneic (ablative or non-myeloablative) hematopoietic cell transplantation experimental and investigational for individuals with myelofibrosis who 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,

CPB 0634 - Non-myeloablative Hematopoietic Cell Transplantation (Mini-Allograft / Reduced Intensity Conditioning Transplant),

http://qawww.aetna.com/cpb/medical/data/800_899/0838_draft.html

12/08/2014
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, cytoressive 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 x 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- cytogenetic
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).

The British Committee for Standards in Haematology’s guidelines for “The diagnosis and management of myelofibrosis” (Reilly et al, 2012) did not mention repeat/second allo-HSCT.

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
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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 x 10⁹ /L, circulating blasts greater than or equal to 1 %, constitutional symptoms, red cell transfusion dependency, platelet count less than 100 x 10⁹ /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.

An UpToDate review on “Prognosis and treatment of primary myelofibrosis” (Tefferi, 2014b) does not mention repeat/second allo-HSCT for patients who relapsed after initial allo-HSCT.

**CPT Codes / HCPCS Codes / ICD-10 Codes**

**CPT codes covered if selection criteria are met:**

- 38204 -
- 38205, 38207
- 38215,
- 38230, 38240,
- 38242

**CPT codes not covered for indications listed in the CPB:**

- 38232
- 38241

**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.

