Primary Myelofibrosis

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Updates:

- New diagnostic Criteria

Introduction

Primary myelofibrosis is also known as idiopathic myelofibrosis, agnogenic myeloid metaplasia or myelofibrosis with myeloid metaplasia. It is a clonal stem cell disorder that results in: ineffective erythropoiesis, dysplastic megakaryocytic hyperplasia, reactive myelofibrosis, and extramedullary hematopoiesis (primarily liver and spleen). The incidence of the disease is 1 in 100,000. The average age at diagnosis is 65 years with 11% of patients less than 45 years at diagnosis. Death usually results from complications of cytopenias (infection, bleeding), thrombosis, congestive heart failure (often from pulmonary hypertension), or acute myeloid leukemia (risk 20% at 10 years). The marrow fibrosis is a result of the nonspecific reaction to the underlying clonal activity; the fibroblasts are not part of the abnormal clone but are stimulated by PDGF, calmodulin, TGFB, and VEGF. There are 3 different forms of the disease – agnogenic myeloid metaplasia (primary), post polycythemic myeloid metaplasia (post polycythemia vera), and post-thrombocythemic myeloid metaplasia (post-essential thrombocythemia). A mutation in the tyrosine kinase Jak2 is found in 50% of patients with myelofibrosis (JAK2617V>F, and exon 14 mutation) [1].

Clinical Presentation

The clinical presentation may include:

- Hepatosplenomegaly (may be associated with diarrhea, peripheral edema, varicosities, ascites from portal hypertension, splenic infarction, and cytopenias from sequestration)
- Progressive anemia
- Hypercatabolic symptoms (weight loss, anorexia, night sweats)
- Leukocytosis/leukopenia (10% present with WBC > 25; 10% WBC < 3)
- Thrombocytopenia (40% present with platelet counts below the normal range, less commonly thrombocytosis)
- Extramedullary hematopoiesis (lymph nodes, serosal surfaces, lungs, urogenital [hematuria], paraspinal)
- Periostitis/hypertrophic osteoarthropathy
- Liver failure (possible etiologies include portal hypertension, transfusional iron overload, hepatic vein thrombosis, portal vein thrombosis, and extramedullary hematopoiesis).

Diagnosis Criteria

The diagnosis requires all 3 major criteria and 2 minor criteria [2]:

Major Criteria	Minor Criteria
1. Presence of megakaryocyte proliferation and atypia, usually with either reticulin or collagen fibrosis; in absence of fibrosis, megakaryocyte changes must be accompanied by an increased bone marrow cellularity (pre-fibrotic cellular phase disease).	1. Leukoerythroblastosis 2. Increase in LDH 3. Anemia 4. Palpable splenomegaly
2. Not meeting WHO criteria for PV (including iron repletion for iron deficient patients), CML, MDS or other myeloid neoplasm.	
3. Demonstration of JAK2617V>F or other clonal marker (eg. MPL515W>L/K) or in the absence of a clonal marker, no evidence of underlying inflammatory or neoplastic disease.	

Prognostic Factors

The median survival ranges from 3.5 to 5.5 years. Adverse prognostic features include: advanced age, anemia, hypercatabolic symptoms, WBC > 10, leukopenia, circulating blasts, platelets < 100, and abnormal karyotype. Patients less than 55 years at diagnosis fair better, with a median survival of 10 years. Recently, the number of circulating CD34+ cell was shown to correlate with the prognostic scoring system, time to blast crisis, and survival. Individuals with CD34+ cells >300 x 10^6/L had a 60% survival at 2 years compared to 95% for patients with CD34+ cells <300 x 10^6/L [3]. JAK2617V>F patients had a significantly poorer survival than patients without the mutation in one retrospective report (adjusted hazards ratio 3.30; 95% confidence interval 1.26 to 8.68; p=0.01) [4].

Prognostic Scoring System [5]

One point for each factor (max = 2)	Median survival for each risk group
1 – Hemoglobin < 100 g/L	0 – Low risk – 93 months
1 – WBC < 4 x 10^9/L	1 – Intermediate risk – 26 months
1 – WBC > 30 x 10^9/L	2 – High risk – 13 months

Differential Diagnosis

- Other myeloproliferative diseases – CML, ET, and PRV
- Myelodysplastic syndromes
- AML – FAB M7
- Metastatic carcinoma
- Hematologic malignancies with bone marrow involvement – NHL, HL, plasma cell dyscrasias, hairy cell leukemia
- Nonmalignant or inflammatory diseases – TB, Paget's disease

Baseline Investigations

- CBC, differential and blood film review
  - Tear dropped shaped erythrocytes, less shifted granulopoiesis, and nucleated red blood cells
- $CD34^+$ cell count
- Chemistry – AST, ALT, ALP, Bilirubin, Albumin
- Abdominal ultrasound
- Bone marrow aspirate (if possible) and biopsy
  - The degree of fibrosis may be small in the early stages of the disease
  - 10% of patients with essential thrombocythemia have a small to moderate amount of fibrosis
- Bone marrow (if possible) or peripheral blood cytogenetics, including PCR for JAK2617V>F and bcr-abl transcript
  - 60% are abnormal in myelofibrosis and abnormal cytogenetics predict an inferior survival (30 months vs. 6 years)
  - Useful in excluding CML
  - Deletions of 5 and 7 are not typical of myelofibrosis and a myelodysplastic syndrome should be considered
  - The most common abnormalities are deletion 13q, trisomy 8, deletion 20q, and trisomy 21

Management

The management of primary myelofibrosis in patients over the age of 60 is palliative. No therapy has been shown to change the natural history of the disease over supportive care alone. Patients less than 60 years of age should be considered as candidates for allogeneic peripheral blood stem cell transplant. In two recent reports totaling 45 patients undergoing allogeneic stem cell transplant for myelofibrosis at a median age of 45 to 48 years, the survival rate was poor (41% at 2 years in one and 39% at 3 years in the other) [6, 7]. Survival was worse for high-risk patients. Small cohort studies suggest that reduced-intensity allogeneic stem cell transplant may be as effective with less toxicity in patients aged 45-60 [8, 9].

Below are suggested management strategies for the palliation of patients with myelofibrosis:

Anemia

Red cell transfusions are the primary management strategy for control of anemia. The hemoglobin should be maintained above 60 to 85 g/L depending on the patient tolerance of anemia. A single transfusion threshold for all patients is not recommended. Patients do not require any specific red blood cell manipulation (i.e. irradiation or CMV-seronegative units). After approximately 20 units of packed red blood cell transfusions, patients expected to survive more than 2 to 4 years, should be screened for iron overload and counseled as to the need for iron chelation therapy. Iron chelation therapy is rarely indicated, as the survival of intermediate risk disease is less than 2 years.

Danazol has been reported to provide transient effects in the management of anemia, however the response rate is less than 30% [10]. Consider for patients with low and intermediate prognostic disease. It is rarely, if ever, effective in patients with advanced disease. The starting dose is 600 mg per day and responses may not be seen until 3 to 6 months after starting therapy. Patients on danazol must be monitored for drug induced liver toxicity.

Alternatively, **erythropoietin** can be considered. It appears to be effective in approximately 30-50% of patients, particularly in patients with serum EPO levels less than 125 mU/mL, women, patients with higher starting hemoglobin, and those patients receiving less than 3 units of red blood cell transfusions per month [11, 12]. The starting dose should be 600 U/Kg per week (maximum dose 40 000 U per week). Rarely, patients experience an exacerbation of splenomegaly with erythropoietin therapy. One report utilized erythropoietin 600 U/kg/week, interferon alpha 3 mU three times per week, and GM-CSF 250 $\mu g/m^2/d$. Five of 7 patients experienced a moderate rise in hemoglobin [13]. Several reports show successful treatment with combination therapy of the above agents. Combinations have included androgen (fluoxymestrone 10 mg po bid or danazol 200-800 mg po od) and erythropoietin [14].

Two phase II studies of **lenalidomide** have been reported. In total, 68 patients were treated with 10 mg daily for 28 days each month for 6 to 24 months. Dosage was reduced to 5 mg/day if the patient's platelet count was less than 100×10^9/L. Major erythroid response was seen in 17%. The most common adverse events were neutropenia (32%) and thrombocytopenia (27%) [15].

There are 9 clinical trials evaluating **thalidomide** [16-24] in small numbers of patients with myelofibrosis (n=12 to 63 patients). The dosage ranged from 50 mg to 800 mg per day. In several of these reports the thalidomide was used in combination with corticosteroids. Anemia responded in 0-62% of patients (median 40%). Similar levels of response were seen in terms of thrombocytopenia and splenomegaly. The long-term response to thalidomide is unclear as the dropout rate was extremely high in many of these reports (> 50% in most). Side effects were substantial, including fatigue, somnolence, neurologic toxicity, and neutropenia. Unusual side effects included thrombocytosis and leukocytosis. Better tolerance was seen in reports of low dose thalidomide (50-100 mg per day) used in conjunction with corticosteroids (prednisone 0.5 mg/kg/d), with drop out rates of approximately 30%. Clinical responses did not correlate with improvements in marrow fibrosis or angiogenesis. The Mayo Clinic does not recommend routine thromboprophylaxis for myelofibrosis patients on thalidomide [14].

Preliminary studies with interferon-alpha, pirfenidone (anti-angiogenesis therapy), anagrelide, suramin, and imatinib mesylate have to date shown no benefit in reduction in cytopenias or transfusion requirements.

Splenomegaly/Organomegaly/Constitutional Symptoms

Front-line therapy should by **hydroxyurea**. It is well tolerated and should be commenced at a daily dose of 15 mg/kg. Patients should be monitored for cytopenias, adverse effects, and response to therapy every 8 weeks.

Second-line therapy should be with **interferon-alpha**. The recommended dose is 3 mU sc three times per week [13]. Patients should be monitored for cytopenias, adverse effects, and response to treatment every 8 weeks.

Third-line therapy for splenomegaly is **splenectomy**. In one large series of 223 patients [25] – splenectomy was associated with: perioperative mortality 9%, morbidity 31% (15% hemorrhage, 9% infection, 7% thrombosis), accelerated hepatomegaly 16%, extreme thrombocytosis 22% (with associated thrombosis). Response at 1 year for the common 4 indications for splenectomy – control of mass effect/constitutional symptoms 67%, portal HTN 50%, transfusion dependency 23%, severe thrombocytopenia 0%. The median survival after splenectomy was 2 years. In a more recent report from the Mayo Clinic, a perioperative morbidity rate of 25% was reported for 314 patients undergoing operative splenectomy between 1976 and 2004 [26]. Post-operative bleeding (14%), thrombosis (10%; vast majority portal vein thrombosis), and infection (10%; most commonly pneumonia) were the most common perioperative complications. Perioperative mortality was 9%. Splenectomy may be recommended for: (1) chemotherapy resistant symptomatic splenomegaly; and (2) complications of portal HTN. Splenectomy should not be utilized in the management of severe thrombocytopenia (response rate 0%) or transfusion dependency (response rate 23%). Preoperatively check PT/PTT, fibrinogen, and D-Dimers. If there is evidence of DIC the risk of perioperative hemorrhage/thrombosis is greater and an attempt to control DIC pre-op with hydroxyurea should be made. One retrospective cohort series found a 2.6 fold risk of AML for patients who had undergone a splenectomy (risk of AML at 12 years – 55% vs. 27% risk) [27].

Fourth-line therapy for splenomegaly is **splenic irradiation**. Consider as a last resort for patients who require splenectomy as above, but operative risk precludes splenectomy. Note: irradiation results in splenic fibrosis and precludes future splenectomy; and, 25% experience profound thrombocytopenia (resulting in death in 13% of patients).

Acute Myeloid Leukemia

The management of leukemic transformation is generally palliative. See secondary AML section.

Follow-Up

Patients should be assessed every 8 to 12 weeks for management, complication of therapy, and complications of the disease.

The routine follow-up should include: history, physical exam, CBC, differential, blood film review, liver function tests, and liver enzymes. Pre-operatively patients should be tested for occult DIC with PT/PTT, D-dimers and fibrinogen.

Supportive Care

Patients should undergo yearly flu vaccination and receive Pneumovax every 5 years.

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