Greater Manchester and Cheshire Cancer Network

# Guidelines for the diagnosis and treatment of primary myelofibrosis, post-essential thrombocythaemia myelofibrosis and post-polycythaemia myelofibrosis

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**Index**

## Introduction

These guidelines will address the diagnosis, prognosis and treatment of patients with

(i) Primary myelofibrosis (PMF);
(ii) Post-essential thrombocythaemia myelofibrosis (post-ET MF); and
(iii) Post-polycythaemic myelofibrosis (post-PV MF).

The many other conditions associated with reticulin or collagen fibrosis of the bone marrow (Kuter et al., 2007) will not be discussed further.

## Primary myelofibrosis

PMF is a clonal neoplasm associated with an abnormal expansion predominantly of megakaryocyte and granulocyte lineages which leads to bone marrow fibrosis and extramedullary haematopoiesis. Evolution of the disease may be progressive with an initial hypercellular phase with minimal fibrosis (up to 30% of patients) followed over time by increasing fibrosis and osteosclerosis. Its incidence approximates to 1 case per 100,000/year with no sex bias and a median age of presentation of around 60 (Thiele et al., 2008).

*Diagnostic criteria*

Diagnosis requires all three major and two minor criteria (Thiele et al., 2008):

MAJOR

(i) Presence of megakaryocyte proliferation and atypia (small to large megakaryocytes with an aberrant nuclear/cytoplasmic ration and hyperchromatic, bulbous, or irregularly folded nuclei and dense clustering), usually accompanied by either reticulin and/or collagen fibrosis; OR in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterised by granulocytic proliferation and often decreased erythropoiesis (i.e. prefibrotic cellular phase disease)**

(ii) Not meeting WHO criteria for polycythaemia vera, *BCR-ABL1*$^{+}$ chronic myeloid leukaemia, myelodysplastic syndrome or other myeloid neoplasm

(iii) Demonstration of *JAK2* V617F mutation or other clonal marker such as *MPL* W515K/L; OR in the absence of a clonal marker, no evidence that the bone marrow fibrosis or other changes are secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukaemia or other lymphoid neoplasm, metastatic malignancy or toxic myelopathies

MINOR

(i) Leucoerythroblastosis

(ii) Increase in serum lactate dehydrogenase (LDH) level

(iii) Anaemia

(iv) Splenomegaly

** 30-40% of patients are diagnosed in the pre-fibrotic phase and 60-70% in the overt fibrotic phase of the disease.

*Clinical and pathological features*

Up to 30% of patients may be asymptomatic at diagnosis, with the condition picked up on a routine blood count (e.g. anaemia, thrombocytosis), chemistry screen (e.g. raised LDH) or examination (e.g. splenomegaly). Others may complain of constitutional symptoms, such as fatigue, dyspnoea, weight loss, night sweats, low-grade fever and pruritis (related to raised levels of proinflammatory cytokines); symptoms related to gout; or symptoms related to splenomegaly, such as early satiety and left upper quadrant discomfort.

Up to 90% of patients exhibit splenomegaly and 50% hepatomegaly.

*Investigations*

Baseline investigations include blood count, blood film (often shows tear drop poikilocytes), renal and liver function tests, LDH, haematinics and *JAK2* V617F mutation status (found in ~50% of patients). Consider *BCR-ABL* analysis if trephine biopsy is atypical, and exclusion of *PDGFRA/B* rearrangements where eosinophilia is noted.

Careful examination of megakaryocyte morphology is essential to distinguish prefibrotic PMF with accompanying thrombocytosis from essential thrombocythaemia. This is because the former mostly evolves in to overt fibrotic/sclerotic PMF whereas the latter mostly does not. Megakaryocytes exhibit significantly greater atypia in the former versus the latter condition.

Karyotype analysis recurrently indicates lesions such as del(13)(q12-22), der(6)t(1;6)(q21-23;p21.3), del(20q), partial trisomy 1q, trisomy 8 and trisomy 9.

The presence of 10-19% $CD34^+$ blasts indicates an accelerated phase of the disease. The presence of 20% or more blasts indicates acute myeloid leukaemia.

**Post-polycythaemia myelofibrosis**

During the later phases of polycythaemia vera the disease may progress to post-polycythaemia myelofibrosis (post-PV MF) in approximately 20% of cases. The red cell mass may normalise and then contract, the blood film may show a leucoerythroblastic picture with tear drop poikilocytes and splenomegaly may develop. The bone marrow may be hypocellular with prominent megakaryocyte atypia and reticulin/collagen fibrosis. Blasts are typically less than 10%; a higher frequency may indicate an accelerated phase of the disease (Thiele et al., 2008b).

*Diagnostic criteria for post-polycythaemia myelofibrosis*

REQUIRED

(i) Documentation of a previous diagnosis of PV (see below)

(ii) Bone marrow fibrosis grade 2-3

ADDITIONAL CRITERIA (two required)

(i) Anaemia or sustained loss of either phlebotomy (in the absence of cytoreductive therapy) or requirement for cytoreduction treatment for erythrocytosis

(ii) Leucoerythroblastosis

(iii) Increasing splenomegaly defined as either an increase in palpable splenomegaly of > 5cm from baseline, or the appearance of newly palpable splenomegaly

(iv) Development of >1 of 3 constitutional symptoms: >10% weight loss in six months, night sweats, unexplained fever >37.5C

*Diagnostic criteria for polycythaemia vera*

Diagnosis required both major criteria and one minor criterion, or one major and two minor.

MAJOR

(i) Haemoglobin >18.5g/dl in men, >16.5g/dl in women or other evidence of increased red cell volume
(ii) Presence of *JAK2* V617F or other functionally similar mutation such as exon 12 mutation

MINOR

(i) BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic and megakaryocytic proliferation
(ii) Serum erythropoietin level below the reference range for normal
(iii) Endogenous erythroid colony formation in vitro

**Post-essential thrombocythaemia myelofibrosis**

ET is typically an indolent disorder characterised by long symptom-free periods interrupted by occasional haemorrhage or thrombosis (Thiele et al., 2008). Evolution to myelofibrosis in ET is uncommon.

It is of note that the early stages of primary myelofibrosis may mimic ET. Careful evaluation of the BM biopsy is essential to distinguish the two conditions which have quite distinct prognoses.

*Diagnostic criteria for post-essential thrombocythaemia myelofibrosis*

REQUIRED

(i) Documentation of a previous diagnosis of ET (see below)

(ii) Bone marrow fibrosis grade 2-3

ADDITIONAL CRITERIA (two required)

(i) Anaemia or > 2g/dl decrease from baseline haemoglobin levels

(ii) Leucoerythroblastosis

(iii) Increasing splenomegaly defined as either an increase in palpable splenomegaly of > 5cm from baseline, or the appearance of newly palpable splenomegaly

(iv) Increased LDH above baseline level

(v) Development of >1 of 3 constitutional symptoms: >10% weight loss in six months, night sweats, unexplained fever >37.5C

*Diagnostic criteria for essential thrombocythaemia*

Diagnosis requires meeting all four criteria.

(i) Sustained platelet count >450x$10^9$/l

(ii) BM biopsy shows proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes. No significant increase or left-shift of neutrophil granulopoiesis or erythropoiesis

(iii) Not meeting WHO criteria for PV, primary myelofibrosis, *BCR-ABL*$^+$ CML, myelodysplasia or other myeloid neoplasm

(iv) Demonstration of *JAK2* V617F or other clonal marker, or in their absence, no evidence of reactive thrombocytosis

**Prognostic scoring systems**

*Note that these prognostic scoring systems are derived from studies which only included patients with PMF, and excluded those with post-PRV or post-ET MF. Caution should be used in the application of these risk stratifications to patients with post-PRV or post-ET MF.*

1) International Working Group of Myelofibrosis Research and Treatment (Cervantes et al., 2009)

Score 1 for each of the following at diagnosis:

(i) age ≥ 65
(ii) presence of constitutional symptoms
(iii) haemoglobin ≤ 10g/dl
(iv) WBC ≥ $25x10^9$/l
(v) Blood blasts ≥ 1%

| Risk group | Score | Median survival (months, 95% CI) |
|---|---|---|
| Low | 0 | 135 (117-181) |
| Intermediate-1 | 1 | 95 (79-114) |
| Intermediate-2 | 2 | 48 (43-59) |
| High | ≥ 3 | 27 (23-31) |

2) Dynamic International Prognostic Scoring System (DIPSS) for PMF (Passamonti et al., 2010)

This is suitable for assessment of prognosis at any time during the clinical course. The acquisition of transfusion dependence (not induced by therapy) is a particularly adverse prognostic feature.

| Prognostic variable | Score 0 | Score 1 | Score 2 |
|---|---|---|---|
| Age, yrs | ≤ 65 | ≥ 65 | |
| WBC, $x10^9$/l | ≤ 25 | ≥ 25 | |
| Haemoglobin, g/dl | ≥ 10 | | ≤ 10 |
| Blood blasts, % | ≤ 1 | ≥ 1 | |
| Constitutional symptoms | No | Yes | |

| Risk group | Score | Median survival (years) |
|---|---|---|
| Low | 0 | not reached |
| Intermediate-1 | 1-2 | 14.2 |
| Intermediate-2 | 3-4 | 4 |
| High | 5-6 | 1.5 |

3) Age adjusted DIPPS for PMF, for patients younger than 65 (Passamonti et al., 2010)

This is particularly useful for assessment of candidates for allogeneic transplantation.

| Prognostic variable | Score 0 | Score 1 | Score 2 |
|---|---|---|---|
| WBC, $x10^9$/l | ≤ 25 | ≥ 25 | |
| Haemoglobin, g/dl | ≥ 10 | | ≤ 10 |
| Blood blasts, % | ≤ 1 | | ≥ 1 |
| Constitutional symptoms | No | | Yes |

| Risk group | Score | Median survival (years) |
|---|---|---|
| Low | 0 | not reached |
| Intermediate-1 | 1-2 | 9.8 |
| Intermediate-2 | 3-4 | 4.8 |
| High | More than 4 | 2.3 |

**Treatment overview**
(Tefferi et al., 2011; Reilly et al., 2012)

Typically, the risk score dictates treatment.

For asymptomatic patients with **low risk** or **intermediate-1 risk** disease, there is currently no evidence to support therapeutic intervention. These patients should be followed on a watch and wait basis, unless specific disease-associated symptoms are troublesome. Management of these is discussed below.

For patients with **high risk** or **intermediate-2 risk** disease, the choice of management strategies lies between allogeneic transplantation and palliation. The only curative treatment for PMF is allogeneic bone marrow transplantation. Non-transplant therapies are palliative, with none to date offering a proven survival benefit. However, the advent of JAK2 inhibitors may change this, with early data and clinical experience looking promising for some patients.

*Allogeneic bone marrow transplantation*

The BCSH recommendations for allogeneic transplantation in myelofibrosis are as follows and apply to those considered fit enough to undergo the procedure, who have an estimated life expectancy of less than five years and an available sibling or matched unrelated donor (Reilly et al., 2012):

Age <45, IPSS INT-2 or high risk – consider for myeloablative BMT (e.g. Bu/Cy or Cy/TBI conditioning)
Age >45, IPSS INT-2 or high risk – consider for reduced intensity BMT (e.g. Flu/TBI (2Gy), Flu/Bu/ALG)

All patients with myelofibrosis should be considered for allogeneic transplant and referred to an appropriate centre for evaluation where appropriate.

It should be noted that typical reported 3-5 year survival rates are 30-50% for MF patients treated with allo BMT. There is variability in transplantation policies at different centres. While in the UK (Reilly et al., 2012) and elsewhere (Tefferi et al., 2011), transplantation is offered to INT-2 and high risk patients, in Boston some INT-1 patients are considered and some higher risk patients are excluded (e.g. those with massive splenomegaly and a significant transfusion history) on the basis that their outcome following transplant is dismal (Bacigalupo et al., 2010; Ballen, 2012).

The role for JAK2 inhibitors either before or following allogeneic BMT is currently unclear and under investigation.

*JAK2 inhibitors*

Given the recurrent mutations in JAK2 in PMF, inhibitors of this kinase have been developed and tested in clinical trials. It is of note that patients appear to respond to therapy with a JAK2 inhibitor whether or not they have a JAK2 mutation.

The JAK2 inhibitor ruxolitinib (US FDA approved, November 2011) is effective in reducing spleen size and improving symptom score in myelofibrosis, both by comparison with placebo and by comparison with best available therapy. The COMFORT-1 and COMFORT-2 trials demonstrated that 30-40% of patients have >35% reduction in spleen volume and about half have a 50% improvement in symptom score. Anaemia and thrombocytopaenia were the most common adverse events; patients with platelet counts lower than 100 x $10^9$/l were excluded. The drug was well tolerated. There is some preliminary evidence for a survival benefit for ruxolitinib treated patients over placebo treated patients in COMFORT-1 (Verstovsek et al., 2012; Harrison et al., 2012).

The only licenced JAK2 inhibitor available to date is ruxolitinib. It is currently (20.5.13) on the National Cancer Drugs Fund List (http://www.england.nhs.uk/ourwork/cdf/) for:

The treatment of symptomatic splenomegaly in primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis where the following criteria are met:

1. a) Intermediate / high risk primary myelofibrosis, OR
   b) Post polycythaemia myelofibrosis, OR
   c) Post essential thrombocytosis myelofibrosis

2. a) 1st line indication, OR
   b) 2nd line indication

3. Symptomatic splenomegaly and/or constitutional symptoms

4. Unsuitable for a stem cell transplant

Of note, ruxolitinib is currently being reviewed by NICE and the preliminary final appraisal determination appears to be that while NICE agrees it is clinically effective, the cost per QALY is £57,000 - £149,000 rendering it cost ineffective. It is not clear whether the NHS will fund this drug once the final NICE guidance is published.

Other JAK2 inhibitors are currently in clinical trials. A Sanofi compound SAR302503 has just completed a successful Phase 3 trial, but is not yet licenced. Pacritinib is currently in phase 3 trials.

This is a fast-moving area of research and recommendations will likely change over the next months and years. However, it seems likely that a significant proportion of patients will benefit at least symptomatically, and possibly with prolonged survival, through treatment with a JAK2 inhibitor. A trial of therapy in INT-2 and high risk patients with troublesome symptoms is recommended.

*Other agents and approaches*

Other therapeutic modalities used in myelofibrosis include hydroxycarbamide, immunomodulatory agents (e.g. thalidomide, prednisolone), splenectomy, radiotherapy, blood transfusion, androgens and erythropoietin. These will be discussed in turn in the next section.

**Management of specific issues**

*Splenomegaly and extramedullary haematopoiesis*

Symptomatic splenomegaly can be treated with a JAK2 inhibitor or anti-proliferative chemotherapy such as hydroxycarbamide (both in the absence of significant cytopaenias). Other agents that may be effective (typical reported response rates are 5-40%) include low dose thalidomide (with or without prednisolone, and to be considered in those with significant cytopaenias) and possibly lenalidomide, low dose melphalan or busulphan.

Splenectomy can be considered in patients with drug-refractory symptomatic splenomegaly, severe hypercatabolism, severe portal hypertension, significant splenic infarction, or refractory haemolysis but is associated with significant morbidity and mortality and should only be undertaken at an experienced centre following careful pre-operative work-up (Reilly et al., 2012). Beneficial responses to splenectomy may include loss of transfusion dependence and improvement in constitutional symptoms.

Splenic irradiation can be considered in patients with platelet counts >50 x $10^9$/l who have failed drug therapy and are not candidates for splenectomy. However, it is typically associated with only a transient response and can induce significant cytopaenia, morbidity and mortality.

Low-dose radiotherapy can be considered for treatment of extramedullary haematopoiesis at other sites, and MF-related bone pain.

*Anaemia*

Where patients have symptomatic anaemia, an inappropriately low level of erythropoietin AND minimal splenomegaly, a trial of erythropoietin or darbopoietin is recommended. Erythropoiesis stimulating agents can exacerbate spleen size in those with significant splenomegaly.

Other agents, each of which has a relatively low response rates, may also be tried:

(i) While many androgens have been tested (e.g. fluoxymesterone 10mg TDS), danazol is the first line androgen of choice, as recommended by the BCSH guidelines. Typical reported initial response rates are 30-50%, but with anticipated side effects of fluid retention, hirsutism, increased libido, derangement of LFTs and hepatic tumours. The recommended starting dose is 200mg OD, increasing to a maximum of 600-800mg per day. The response should be assessed at six months with subsequent titration down to the minimum dose required to maintain that response. LFTs should be checked monthly with a liver USS every six months. Male patients should be screened for prostate cancer before therapy and regularly thereafter.

(ii) Thalidomide (e.g. 50mg/day) with or without prednisolone (e.g. 10-20mg/day). This should be avoided in women of child bearing age, those with neuropathy and those with diabetes or osteopaenia. Aspirin should be co-prescribed to minimise risk of thrombosis. Lenalidomide is not recommended. Pomalidomide is currently under evaluation.

Otherwise, transfusion is recommended for symptomatic anaemia, but routine iron chelation is not.

*Constitutional symptoms*

These are probably best managed with a JAK2 inhibitor.

*Minimising thrombotic risk*

For patients with a platelet count >450x$10^9$/l, there is likely an increased thrombotic risk. Here treatment with hydroxycarbamide and aspirin is warranted, together with modification of cardiovascular risk factors (e.g. control blood pressure, advice to stop smoking, treat hypercholesterolaemia, and optimise diabetic control).

Anagrelide should be used with considerable caution given its association with bone marrow fibrosis.

Use of interferon in MF has been associated with high rates of toxicity; however some small studies have reported some benefit. It is recommended to use IFN only in early disease with proliferative features.

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