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## **SECTION 8**

# GUIDELINES FOR MANAGEMENT OF MYELOPROLIFERATIVE DISORDERS

## DEFINITIONS

### Proposed Diagnostic Criteria for Myeloproliferative Diseases (MPD) with JAK2 Mutation

**JAK2-positive thrombocythaemia** (diagnosis requires the presence of all three criteria)

A1. Platelet count  $>450 \times 10^9/L$

A2. Mutation in JAK2, CAL-R or MPL

A3. No other myeloid cancer, BCR-ABL negative, especially JAK2-positive polycythemia, myelofibrosis, or myelodysplasia

**JAK2-positive polycythaemia** (diagnosis requires the presence of both criteria)\*

A1. High hematocrit ( $>52\%$  in men or  $>48\%$  in women) or an increased red cellmass ( $>25\%$  above predicted value)

A2. Mutation in JAK2 or EXON 12

\* Dual pathology (secondary erythrocytosis or relative erythrocytosis) might rarely coexist with a JAK2-positive myeloproliferative disorder. In this situation, it would be prudent to reduce the haematocrit to the same targets as those for polycythaemia vera.

**JAK2-positive myelofibrosis** (diagnosis requires the presence of A1 and A2 and any two B criteria)

A1. Reticulin grade 3 or higher (on a 0–4 scale)

A2. Mutation in JAK2, CAL-R or MPL

B1. Palpable splenomegaly

B2. Otherwise unexplained anaemia (haemoglobin  $<11.5$  g/dL for men;  $<10$  g/dL for women)

B3. Teardrop red cells on peripheral blood film

B4. Leukoerythroblastic blood film (presence of at least 2 nucleated red cells or immature myeloid cells in peripheral blood film)

B5. Systemic symptoms (drenching night sweats, weight loss  $>10\%$  over 6 months, or diffuse bone pain)

B6. Histologic evidence of extramedullary haematopoiesis

#### **JAK2 positive clinically occult MPD**

Patient present with thrombotic problems but without abnormal blood counts and are JAK2 positive. There is limited evidence to guide treatment in this group though it is increasingly recognised. Some consider anticoagulation sufficient and some groups recommend a reduction in platelet count

## Proposed Diagnostic Criteria for MPD without JAK2 Mutation.

**JAK2-negative polycythaemia vera** (diagnosis requires the presence of A1, A2, and A3, plus either another A or two B criteria)

- A1. Increased red-cell mass (>25% above predicted value) or a haematocrit  $\geq 60\%$  in men or  $>56\%$  in women
- A2. Absence of mutation in JAK2
- A3. No causes of secondary erythrocytosis (normal arterial oxygen saturation and no elevation of serum erythropoietin)
- A4. Palpable splenomegaly
- A5. Presence of acquired genetic abnormality (excluding BCR-ABL) in haematopoietic cells
  
- B1. Thrombocytosis (platelets  $>450 \times 10^9/L$ )
- B2. Neutrophilia (neutrophils  $>10 \times 10^9/L$ ;  $>12.5 \times 10^9/L$  in smokers)
- B3. Splenomegaly on radiography
- B4. Endogenous erythroid colonies or low serum erythropoietin

**JAK2-negative essential thrombocythaemia** (diagnosis requires the presence of all five criteria)

- A1. Platelet count  $>600 \times 10^9/L$  on two occasions at least 1 month apart\*
  - A2. Absence of mutation in JAK2
  - A3. No reactive cause for thrombocytosis
  - A4. Normal ferritin ( $>20 \mu g/L$ )
  - A5. No other myeloid disorder, especially chronic myeloid leukaemia, myelofibrosis, polycythaemia vera, or myelodysplasia
- \* The platelet threshold is preferred in patients without the JAK2 mutation, given the difficulty in ruling out reactive thrombocytosis and the fact that 2.5% of persons without a myeloproliferative disorder have a platelet count above the normal range.

**JAK2-negative idiopathic myelofibrosis** (diagnosis requires the presence of A1, A2, A3, and any two B criteria)

- A1. Reticulin grade 3 or higher (on a 0–4 scale)
- A2. Absence of mutation in JAK2
- A3. Absence of BCR-ABL fusion gene
  
- B1. Palpable splenomegaly
- B2. Otherwise unexplained anaemia (haemoglobin  $<11.5 \text{ g/dL}$  for men or  $<10 \text{ g/dL}$  for women)
- B3. Teardrop red cells on peripheral blood film
- B4. Leukoerythroblastic blood film (presence of at least 2 nucleated red cells or immature myeloid cells in peripheral blood film)
- B5. Systemic symptoms (drenching night sweats, weight loss  $>10\%$  over 6 months, or diffuse bone pain)
- B6. Histologic evidence of extramedullary haematopoiesis

**From UK BCSH amended guidelines for diagnosis of Polycythaemia Vera (McMullin, M.F et al BJH and BCSH website) and from Campbell and Green N Engl J Med 2006;355:2452-66**

# POLYCYTHAEMIA VERA (PRV)

## INVESTIGATION OF POLYCYTHAEMIA (ERYTHROCYTOSIS)

Persistently raised haematocrit: 52% ( $\approx 17$ g/dL) – adult male  
48% ( $\approx 16$  g/dL) – adult female

### Causes

1. JAK 2 V617F-positive MPD
2. JAK2 exon 12-positive polycythaemia
3. JAK 2-negative MPD
4. Hypoxia
  - a) Right to left cardiac shunt
  - b) Lung disease / smoking / nocturnal sleep apnoea
5. Inappropriate erythropoietin (Epo) secretion
  - a) Renal , uterine, cerebellar or other tumour
  - b) Post-renal transplant polycythaemia/polycystic kidney disease
  - c) Self-administered erythropoietin
6. Hypoxia sensing disorder (eg. VHL-Chuvash Erythrocytosis, HIF2a abnormalities) - High or normal Epo levels
7. Epo sensing disorder (eg. EpoR) - Low Epo levels
8. High oxygen affinity haemoglobin
9. Red cell membrane or enzyme disorder with low 2,3 DPG
10. Spurious or apparent polycythaemia due to reduced plasma volume
11. Idiopathic erythrocytosis

### First line investigations

If there is a clear and sufficient cause of polycythaemia, eg. cyanotic heart disease or significant respiratory disease, investigate and refer for that condition as appropriate. If the cause is not apparent consider investigation as follows at the first visit.

- FBC, serum vitamin B<sub>12</sub>, red cell/serum folate and serum ferritin
- Biochemistry profile including LDH
- JAK2V617F mutation analysis (1 x EDTA to Molecular Diagnostics, Haematology RVI)
- Epo level (1x EDTA to Haematology, FreemanHospital or 1x clotted sample to JamesCookUniversityHospital)
  - Normal Epo levels using a typical assay range from 3.1 to 16 mIU/mL with a geometric mean of about 8 mIU/mL.
  - An Epo level below 2 IU/mL is nearly always due to PV; however 50% of PV cases will have a level between 2 and 12 IU/mL.
  - A high Epo level >16 IU/mL in a patient with a high Hb indicates secondary polycythaemia.
  - Patients with secondary polycythaemia rarely have Epo levels below the normal range despite the high Hb.
  - Epo levels in between are less helpful.
  - Epo levels must be interpreted with concurrent Hb concentration.

- Epo does show daily variation by as much as 60% of the lowest value with the lowest values typically being found in the morning and early afternoon, and higher values in the later afternoon and evening. Peak levels in those with respiratory disease are often in the early hours of the morning.

## Further investigations

### A. If JAK2 mutation is positive, the diagnosis is of JAK2+ve polycythaemia vera (PV).

- Consider ultrasound of spleen as baseline investigation.

### B. If JAK2 mutation is negative and EPO level low, the diagnosis could be JAK2-negative PV, apparent/spurious polycythaemia or Epo receptor abnormality

- Red cell mass (RCM) is recommended, but is not necessary if Hct is >0.60 in males and >0.56 in females.
- If raised RCM is confirmed or Hct above these limits, proceed to bone marrow examination and ultrasound scan of abdomen.
- If bone marrow is suggestive of primary polycythaemia, request, via haematology at the RVI, a test for Exon 12 mutations that can be done by Newgene on stored DNA following a negative JAK2 v617f assay. A new sample should not be required.
- If still no cause found, and especially if there is a family history of polycythaemia, consider Epo receptor mutation analysis.
- Exon 12 mutation PV typically reported to have 'normal platelet count and marrow showing moderate hypercellularity with erythroid hyperplasia but without megakaryocytic or granulocytic changes seen in other MPD.' (JAK2 exon 12 mutations in PV and Idiopathic erythrocytosis. Scott LM et al NEJM 2007; 356: 459-68.)
- It may be worth repeating the Epo level if overall picture does not fit with PV.

### C. If JAK2 mutation is negative and Epo level high, the diagnosis is secondary polycythaemia

- CXR, blood gasses, SaO<sub>2</sub>, sleep study if necessary
- Ultrasound scan of abdomen for renal tumours/cysts
- Hb HPLC or Hb NMR studies at Leeds (may be arranged via Haematology Specials Laboratory RVI),
- Hb-O<sub>2</sub> saturation studies if altered affinity Hb suspected, eg familial polycythaemia
- von Hippel Lindau gene analysis, ?PHD2 mutation analysis (Arrange via the Department of Haematology, BelfastUniversity, see below)

### D. If JAK2 mutation is negative and Epo normal, the diagnosis of either PV or secondary polycythaemia cannot be excluded.

- Consider repeating Epo level.

- RCM and plasma volume studies are recommended if Hct males <0.60, females <0.56 to exclude apparent polycythaemia.
- If raised RCM is confirmed and secondary polycythaemia is still a possible diagnosis, especially with Epo at high end of normal range, investigate as for JAK2 mutation negative and high Epo initially (see **C** above).
- If Epo level is low normal, investigate as for JAK2 negative and low Epo (see **B** above). It may be necessary to investigate both possibilities.

## TREATMENT OF POLYCYTHAEMIA VERA

### Venesection

- Venesect to Hct of 0.45.
  - Hct of 0.45 equates to a Hb of 15 g/dL, 0.50 to Hb 16.6g/dL. It is possible that the Hb is more reliable than Hct.
- Blood should be venesected over 15 min or more to a maximum of 7mL/kg, i.e. 400 mL in < 60 kg, ≈ 500 mL in 70 kg, ≈ 650mL in 90 kg using likely lean body weight.
- Isovolaemic dilution (500 mL of 0.9% sodium chloride either concurrently or immediately after venesection) may be preferable if
  - the aim is to produce rapid reduction of Hb (equilibration after venesection takes 36-48 hrs and in patients with PV with a markedly raised total blood volume there may be little reduction in Hct until several venesections have been performed).
  - the patient is considered to be at relatively high risk of thrombosis, eg. recent thrombosis or ischaemic cardiac history.
- In new cases blood may be venesected daily or on alternate days to reach a 'safe' Hb. Isovolaemic dilution is recommended when intensive venesection is undertaken.

### Hydroxycarbamide (HC)

Indications to start HC according to BCSH Guidelines are

- poor tolerance of venesection,
- symptomatic or progressive splenomegaly,
- weight loss or night sweats suggesting disease progression, and
- thrombocytosis.

Finzzi & Barbui\* suggested dividing patients into risk categories and treating with HC if high risk as for ET.

- High risk = previous thrombosis, age > 60
- Intermediate risk = age < 60 with cardiovascular risk factors e.g. diabetes, smoking etc.

This would probably lead to more patients being treated with HC.

*\*Finazzi, G. & Barbui, T. (2007) How I treat patients with polycythemia vera. Blood, 109, 5104-5111*

### ELN and IWG-MRT criteria for Hydroxycarbamide resistance and intolerance (Ref: Barbui T et al –JCO, 2011;29:761-770)

**HU resistance** is defined as **anyone of the following criteria-** (after 3 months of >2g/d of HU)

Need for phlebotomy to keep Hct <45% **or**

Uncontrolled Myeloproliferation i.e platelet count  $>400$  and WBC count  $> 10 \times 10^9/L$   
**or**  
Failure to reduce massive splenomegaly by  $>50\%$  as measured by palpation or failure to relieve symptoms related to splenomegaly

**HU intolerance** is defined **as either of the following criteria -**

ANC less than  $1.0 \times 10^9/l$  or platelet count  $< 100 \times 10^9$  or Hb  $< 100$  at the lowest dose of HU required to achieve complete or partial clinicohaemological response or Presence of leg ulcers or other unacceptable HU related non haematological toxicities such as mucocutaneous manifestations, GI symptoms, pneumonitis or fever at any dose of HU.

Treatment Options:

- Interferon-Alpha or PEG Interferon Alpha
- Busulphan ( Increased risk of leukemic transformation)
- Adding anagrelide?
- JAK 2 inhibitor – **if fulfils- NICE criteria**

## **TREATMENT OF OTHER FORMS OF POLYCYTHAEMIA**

### **Apparent or spurious erythrocytosis**

- Confirm raised Hct with two counts at least 3 months apart
- Advise reduction of ethanol, smoking cessation, avoidance of diuretics, avoidance of excessive caffeine intake and control of hypertension.
- Consider venesection if Hct  $>0.54$ , recent history thrombosis, strong risk factors for thrombosis. If thrombotic events occur despite this target, venesect to 0.45.
- Monitor untreated patients.

### **Idiopathic erythrocytosis**

- Treat as for apparent erythrocytosis

### **High oxygen affinity Hb**

- Venesect if symptoms possibly due to high Hb. eg. dizziness, dyspnoea, angina (?to Hct 0.6).
- Venesect if one or more previous thrombotic episodes (?to Hct 0.6).
- If symptoms or events at Hct  $< 0.6$  consider venesection to 0.52.
- Consider partial red cell exchange for major surgery if Hct  $>0.6$ .

### **Hypoxic pulmonary disease**

- Refer to respiratory physicians for consideration O2 therapy
- If there are hyperviscosity symptoms or Hct > 0.56, venesect to 0.5-0.52
- Consider ACE or angiotensin inhibitors.

### **Cyanotic heart disease**

- Isovolaemic venesection when the patient has symptoms of hyperviscosity (dizziness, headache, etc.).
- Target Hb should be individualised to the patient as most of them tolerate very high Hcts >60
- Avoid excessive venesection with iron deficiency which may increase viscosity while compromising O2 delivery.

### **Post Renal transplant erythrocytosis**

- Avoid dehydration.
- Treat with ACEI or angiotensin II receptor antagonist
- Venesect to Hct of 0.45.

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## **ESSENTIAL THROMBOCYTHAEMIA**

### **BCSH 2015 - Proposed diagnostic criteria for essential thrombocythaemia.**

#### **Diagnosis requires A1–A3 or A1 + A3–A5**

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A1 - Sustained platelet count  $\geq 450 \times 10^9/l$

A2 - Presence of an acquired pathogenetic mutation (e.g. in the *JAK2*, *CALR* or *MPL* genes)

A3 - No other myeloid malignancy, especially PV, PMF, CML or MDS

A4 – No reactive cause for thrombocytosis and normal iron stores

A5 - Bone marrow aspirate and trephine biopsy showing increased megakaryocyte numbers displaying a spectrum of morphology with predominant large megakaryocytes with hyperlobated nuclei and abundant cytoplasm.

Reticulin is generally not increased (grades 0–2/4 or grade 0/3)

- Polycythaemia vera; excluded by a normal haematocrit in an iron-replete patient.<sup>b</sup>
- Primary myelofibrosis; indicated by presence of significant marrow bone marrow fibrosis (greater or equal to 2/3 or 3/4 reticulin) AND palpable splenomegaly, blood film abnormalities (circulating progenitors and tear-drop cells) or unexplained anaemia (Barosi, [1999](#); Mesa *et al*, [2007](#)).<sup>c</sup>
- Chronic myeloid leukaemia; excluded by absence of *BCR-ABL1* fusion from bone marrow or peripheral blood.<sup>d</sup>

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## BCSH 2015 - Proposed diagnostic criteria for essential thrombocythaemia.

### Diagnosis requires A1–A3 or A1 + A3–A5

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- Myelodysplastic syndrome; excluded by absence of dysplasia on examination of blood film and bone marrow aspirate

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Check history, Hb, ESR, CRP and fibrinogen. If inflammatory markers (especially fibrinogen) are not raised and if Hb is normal or high normal, essential thrombocythaemia (ET) is likely.

Molecular tests: Peripheral blood JAK2 V617F mutation, MPL W515L mutation, CAL- R, BCR-ABL.

The following are considered atypical features for the diagnosis of ET.

- anaemia without iron deficiency
- poikilocytosis
- leucocytosis
- monocytosis
- blasts
- marked splenomegaly

#### **A. JAK2-positive or MPL or CAL-R mutation positive with no atypical features**

This is diagnostic of ET and bone marrow biopsy is not necessary.

#### **B. JAK2-positive or MPL mutation positive with atypical features**

Possible diagnoses are myelofibrosis (MF), JAK2-positive RARS with thrombocytosis, and JAK2-positive CMML. Bone marrow examination with or without cytogenetics is indicated

#### **C. JAK2-negative and MPL mutation negative and platelets $>600 \times 10^9/L$**

If inflammatory markers are negative and Hb are normal, ET is likely/possible. Please note that ET is not necessarily excluded even if inflammatory markers are positive.

### **JAK2 and other conditions with thrombocytosis**

- RARS with thrombocytosis: 30-50% of these patients will also be found to have the JAK2 mutation.
- CMML with JAK2 mutation: 5-10% of CMML will have the JAK2 mutation.
- AML: <5% of AML cases will have the JAK2 mutation. The majority will have a known pre-existing MPD.

## RISK STRATIFICATION IN ET

- High risk: Age > 60, previous thrombosis or platelets >1500x10<sup>9</sup>/L
- Intermediate risk: Age 40-60. No high risk features
- Low risk: Age <40.No high risk features

Diabetes mellitus, hypertension, renal failure, hyperlipidaemia, smoking, family history, JAK2 and MPL mutation and known thrombophilia may all be considered as risks likely to interact.

## TREATMENT OF ESSENTIAL THROMBOCYTHAEMIA

### Low risk

- Aspirin 75mg od alone.
- Reassess at age 40.

### Intermediate risk

- IF NO Cardiovascular risk factors - aspirin single agent 75mg od. If strong cardiovascular risk factors discuss addition of Hydroxycarbamide with patient
  - The PT1 intermediate arm study used a different definition for intermediate group. Intermediate arm inclusion criteria – Platelet (current or previous) count more than 1500, Previous Ischaemia, thrombosis or embolism or Haemorrhage complication due to ET, Diabetes or Hypertension. According to this study delaying introduction of Hydroxycarbamide till other indications developed did not affect Overall survival, or risk of vascular complications or risk of progression to MF or Acute Leukemia. Also hydroxycarbamide was found to be safe and without increased risk of leukemogenesis if introduced early
  - The trial had started recruiting before the mutations associated with ET were part of standard diagnostic criteria. (final paper publication awaited and may influence recommendation)
- Italian consensus guidelines (Barbui et al. 2004. Haematologica, **89**;215-32) suggest platelets >1000x10<sup>9</sup>/L plus another vascular risk factor as indications for cytoreductive treatment plus aspirin.

### High risk

- Cytoreductive treatment plus aspirin. HC (start 0.5-1 g daily depending on patient size) is the preferred cytoreductive treatment.
- If HC is not tolerated (see side-effects) or platelet count is inadequately controlled, try:
  - Anagrelide\*
  - anagrelide plus HC
  - interferon alfa in younger patients
  - busulfan or <sup>32</sup>P in patients >75years
  - aspirin alone (if there are no history of and no additional risk factors for thrombosis, thrombocytosis is longstanding, and platelets < 1000x10<sup>9</sup>/L)

***\*Anagrelide was less effective at preventing arterial events, chiefly TIAs in the PT-1 trial, and was associated with more progression to MF, greater withdrawal due to side-effects (35% vs 20% for HC). However, it was associated with fewer venous thrombotic events though more gastrointestinal bleeds, perhaps due to the antiplatelet effect of anagrelide in addition to aspirin.***

***If using Anagrelide perform baseline marrow biopsy and repeat 2-3 yearly for assessment of reticulin fibrosis. If fibrosis is increasing then stop anagrelide and seek alternative agents.***

Aspirin and bleeding risk: If the platelet count is  $>1500 \times 10^9/L$  do not start aspirin unless there is active or recent thrombosis. Bleeding may be a greater risk due to acquired von Willebrand disease from adsorption of HMW vWF multimers by the platelet mass. Once the platelet count is  $<1500 \times 10^9/L$ , aspirin should be started unless there have been bleeding complications.

Treatment aim: The target platelet count should be  $<450 \times 10^9/L$ . Some suggest  $<600 \times 10^9/L$  may be adequate especially given that there is no clear relationship between platelet count and thrombotic episodes. Once a stable platelet count has been achieved, follow-up FBC should be not less than 3 to 4 monthly. MPL gene mutation carries slight increased risk of thrombosis

Young patients: Patients of age  $<40$ . Most authorities recommend interferon alfa or anagrelide due to the uncertainty about the very longterm effects of hydroxycarbamide and residual concern regarding leukaemogenicity.

Pregnancy and family planning: Advise against conception on HC or any alkylating agent. Use interferon alfa instead. If further advice is required, contact Dr Claire Harrison at St Thomas's Hospital.

## MYELOFIBROSIS (MF)

**Table II.** Diagnostic criteria for primary myelofibrosis: diagnosis requires A1 + A2 and any two B criteria.

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A1	Bone marrow fibrosis $\geq 3$ (on 0–4 scale).
A2	Pathogenetic mutation (e.g. in <i>JAK2</i> or <i>MPL</i> ), or absence of both <i>BCR-ABL1</i> and reactive causes of bone marrow fibrosis
B1	Palpable splenomegaly
B2	Unexplained anaemia
B3	Leuco-erthroblastosis
B4	Tear-drop red cells
B5	Constitutional symptoms*
B6	Histological evidence of extramedullary haematopoiesis

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\*Drenching night sweats, weight loss >10% over 6 months, unexplained fever (>37.5°C) or diffuse bone pains.

**Table III.** Diagnostic criteria for post-PV and post-ET myelofibrosis: diagnosis requires A1 + A2 and any two B criteria.

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A1	Bone marrow fibrosis $\geq 3$ (on 0–4 scale)
A2	Previous diagnosis of ET or PV
B1	New palpable splenomegaly or increase in spleen size of $\geq 5$ cm
B2	Unexplained anaemia with 20 g/l decrease from baseline haemoglobin
B3	Leuco-erythroblastic blood film.
B4	Tear-drop red cells
B5	Constitutional symptoms*
B6	Histological evidence of extramedullary haematopoiesis.

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\*Drenching night sweats, weight loss >10% over 6 months, unexplained fever (>37.5°C) or diffuse bone pains.

- Bone marrow biopsy is an essential test.
- Testing for JAK2, CAL-R, MPL gene mutations
- BCR-ABL should be routinely tested.
- In the presence of significant eosinophilia, PDGFRA and PDGFRB rearrangements should be tested to exclude chronic eosinophilic leukaemia (see below).

## RISK STRATIFICATION IN MYELOFIBROSIS

Historically the Lille scoring system was widely used: Hb <10 g/dL score 1. WCC <4 x10<sup>9</sup>/L or >30 x10<sup>9</sup>/L score 1

Score	Risk group	Cases (%)	Median survival
0	Low	47	93 months
1	Intermediate	45	26 months
2	High	8	13 months

*Dupriez B, Morel P, Demory J-L et al. (1996) Prognostic factors in agnogenic myeloid metaplasia: a report on 195 cases with a new scoring system. Blood 88, 1013-1018.*

The Lille score has been superceded by several more scoring systems: the International Prognostic Scoring System (IPSS, 2009), Dynamic IPSS (DIPSS, 2010) and DIPSS Plus (2011).

Variable	IPSS	DIPSS
Age >65 years	√	√
Constitutionals symptoms	√	√
Hb <100g/l (or 10g/dl)	√	√
WBC >25	√	√
Circulating blasts ≥1%	√	√
	1 point each	1 point each but Hb=2
DIPSS=plus add 1 point to the DIPSS risk group in addition for:		
<ul style="list-style-type: none"> <li>• Platelet count &lt;100</li> <li>• RBC transfusion need</li> <li>• Unfavourable karyotype +8, -7/7q-, i(17q), inv(3), -5/5q-, 12p-, 11q23 rearrangement</li> </ul>		

Risk Group	IPSS		DIPSS		DIPSS-plus	
	No of factors	Med survival (yrs)	No of factors	Med survival (yrs)	No of factors	Med survival (yrs)
Low	0	11.3	0	Not reached	0	15.4
Intermediate 1	1	7.9	1 or 2	14.2	1	6.5
Intermediate	2	4.0	3 or 4	4	2-3	2.9

2						
High	>=3	2.3	5 or 6	1.5	>=4	1.3

**COMFORT trials defined constitutional symptoms as – weight loss more than 10% of baseline in year preceding diagnosis and/or unexplained fever or excessive sweats persisting for more than 1 month ( appendix 2 COMFORT trial paper NEJM)**

## TREATMENT OF MYELOFIBROSIS

### Options

**Supportive care:** with red cell transfusion

### **Cytoreductive agents:**

**Hydroxycarbamide** – If does not fulfil criteria for use of Ruxolitinib. (Please note that in the MRC-PT1 trial anagrelide was associated with more rapid progression in marrow fibrosis compared to HC.)

**Ruxolitinib:** The JAK1 and JAK2 inhibitor, Ruxolitinib (marketed in the UK by Novartis as Jakavi) has been compared against placebo, or best available therapy in the COMFORT 1 and COMFORT2 studies, respectively. The BCSH guidelines 2015 - currently recommend Ruxolitinib as

**First line therapy** for symptomatic splenomegaly and/or myelofibrosis-related constitutional symptoms regardless of *JAK2* V617F mutation status (*evidence grade 1A*).

Ruxolitinib is NICE approved for the following population:

Ruxolitinib is recommended as an option for treating disease-related splenomegaly or symptoms in adults with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis, only:

- in people with intermediate-2 or high-risk disease.

**'Thal-Pred' regime:** (thalidomide 50 mg o.d. for 6 months PLUS prednisolone 0.5 mg/kg o.d. tapering over 3months) from the Mayo Clinic may be associated with moderate responses in the platelet count (75%), Hb (60%) and spleen size (20%).

**Splenectomy:** is indicated for mechanical symptoms affecting the gastrointestinal tract, pain from distension or infarction, portal hypertension, and cytopenias especially transfusion-dependant anaemia. Splenectomy does not appear to improve survival but may improve quality of life.

- The largest published series of 223 patients from the Mayo Clinic reported a 9% early mortality and 30% post-operative morbidity. 16% of patients went on to develop significant hepatomegaly but this did not appear to affect overall survival and was not predictable. 22% developed platelet counts of  $>600 \times 10^9/L$  and 6%  $>1000 \times 10^9/L$ . Of these, 19% (4% of total) died of bleeding or thrombosis. Hypo- or normo-cellular bone marrow correlated with poorer survival. Marked thrombocytopenia' (not defined) preoperatively was associated with a short survival.
- Relative contra-indications to splenectomy are marked preoperative thrombocytopenia ( $< 20 \times 10^9/L$ ) or thrombocytosis ( $>2500 \times 10^9/L$ ) and bone marrow that is not hypercellular.
- Before operation repeat bone marrow biopsy to assess cellularity and perform doppler ultrasound to check for intrahepatic thrombosis (Budd-Chiari syndrome) before proceeding as this preferentially requires porto-systemic shunt instead or as well (refer to the Liver Team at Freeman Hospital for assessment in this case). Try to bring platelets well within normal range if raised.

**Splenic irradiation:** can produce temporary alleviation of symptoms. It does not prevent future splenectomy but is reported to increase operative bleeding. It may be followed by prolonged cytopenia.

**Allogeneic Haemopoietic Stem Cell Transplant:** See Indications for Haemopoietic Stem Cell Transplantation.

**New Drugs: Newer Jak2 inhibitors.** Centres in Sheffield (Professor John Reilly), Cambridge (Professor Anthony Green) and Belfast (Professor Mary-Francis MacMullin) may offer advice/trial treatment to patients with progressive MF.

## **NOTES RELEVANT TO MANAGEMENT OF ANY MPD**

### ***Side- effects of HC***

- Patients should be counselled that HC is unlikely to be leukaemogenic and that the risk of secondary acute leukaemia is very small.
- Drug fever with abnormal LFTs is uncommon but indicates stopping of the drug.
- Dry skin, mild non-specific skin rash, mouth ulcers (2% in MRC-PT1 trial) may occur. If not severe, HC can be continued.
- Ankle ulcers. (5% in PT1 trial) are nearly always on the external malleolus and are deep and painful. A red reticular rash over the toes, also with pain, is a common accompaniment. The features are often mistaken for vascular insufficiency. Stopping HC causes resolution of the ulcer(s) over a few months but the pain usually settles first. The lesions on the toes may be slower to remit. The mechanism of this is not known. It has also been rarely reported in patients on anagrelide. Patients often are referred to vascular surgeons before the problem is brought to the attention of the haematologist.

- There is an increased risk of skin cancers in patients treated with HC. Appropriate minimisation of sun exposure should be recommended along with increased vigilance for skin changes.

### ***Side-effects of anagrelide***

- Cardiovascular events: chiefly palpitations (16%) and less commonly cardiac failure (3.5% vs 1.75% for HC in PT1 trial)
- Gastrointestinal effects: bleeding (3%), diarrhoea, abdominal pain
- Headaches, bloating, fluid retention, 'constitutional' symptoms.

### ***Thrombosis and JAK2***

- Splanchnic vein thrombosis is an increasingly recognised complication of MPD which is often occult at the time of diagnosis. It occurs in younger patients especially women. 50% or more of patients with Budd-Chiari syndrome are associated with JAK2-positive MPD, usually with erythroid and platelet involvement rather than plain ET. JAK2-negative MPD is relatively infrequent. The prognosis after Budd-Chiari syndrome is surprisingly good if patients are treated with HC plus warfarin or plus aspirin or both.
- A number of cases of cerebral sinus vein thrombosis ( $\approx 6\%$ ) are similarly associated with JAK2-positive MPD.

### ***Systemic Mastocytosis***

- The diagnosis should be suspected if there are dermatographism and/or recurrent or unusual anaphylactic reactions. Measure serum tryptase and repeat serum tryptase after recovery from anaphylaxis if suspicious. Levels of  $> 20 \mu\text{g/L}$  are suspicious and warrant further investigation. Enquire Immunology at RVI for this test (serum sample). Bone Marrow trephine (including stains for mast cell tryptase) should show diagnostic features. C-KIT mutation analysis may be performed via Cytogenetics/Newgene at the Centre for Life on bone marrow aspirate or on trephine section recovered DNA. Patients negative for the common c-Kit mutation may be effectively treated with low dose tyrosine kinase inhibitor (Imatinib).
- Advanced Systemic Mastocytosis – Midostaurin has been found to be effective in an open label study. Assess to Midostaurin for this indication will need clarification. (N Engl J Med 2016; 374:2530-2541)

### ***Eosinophilia***

- Moderate eosinophilia =  $1.5\text{-}5 \times 10^9/\text{L}$
- Severe eosinophilia =  $>5 \times 10^9/\text{L}$

Eosinophilia may be a reactive, familial or acquired clonal disorder.

Reactive causes: Worms and flukes, toxoplasmosis, borreliosis, HIV infection, atopic/allergic conditions including drug reactions, Churg-Strauss syndrome,

Wegener's granulomatosis, polyarteritis nodosa and sarcoidosis, Hodgkin lymphoma, or solid cancers, may produce extreme eosinophilia.

Familial eosinophilia: is very rare.

Acquired clonal disease: Chronic eosinophilic leukemia is associated with platelet-derived growth factor receptor alpha (PDGFRA) or beta (PDGFRB) abnormalities, c-kit mutations and 8p11 syndrome with rearrangement of fibroblast growth factor receptor-1 gene. PDGFRA abnormalities frequently arise from an interstitial deletion of chromosome 4 (4q12) which produces a constitutionally activated tyrosine kinase. These particular patients may be effectively treated with Imatinib at doses much smaller than those normally used in the treatment of chronic myeloid leukaemia.

### ***Patient websites and associations***

MPD-support website: [www.mpdvoice.org.uk](http://www.mpdvoice.org.uk)

### ***Addresses/contacts***

- JAK2V617F mutation, JAK2 exon 12 mutation and ML gene analysis (1 x EDTA to Newgene via the Haematology laboratory at the RVI)
- Epo level (1x EDTA to Haematology, FreemanHospital or 1x clotted sample to JamesCookUniversityHospital)
- VHL gene, Epo receptor gene and other inherited causes of polycythaemia. Professor Mary-Francis MacMullin, Consultant Haematologist, or Dr Melanie Percy, ClinicalScientist, ([melanie.percy@belfasttrust.hscni.net](mailto:melanie.percy@belfasttrust.hscni.net)) Department of Haematology, C Floor, Tower Block, Belfast City Hospital Lisburn Road, Belfast BT9 7AD (phone: 028 90 263733)

### ***References***

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