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Guidelines for the diagnosis and treatment of myeloproliferative neoplasms including:

Polycythaemia vera

Essential thrombocythaemia

and

Myelofibrosis

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1. Polycythaemia vera — Rowena Thomas-Dewing

Polycythaemia vera (PV) is a chronic myeloproliferative neoplasm (MPN) characterised predominantly by erythrocytosis. It is associated with *JAK2* mutations (V617F or exon 12) in almost all cases. Sixty percent of PV patients are >60 years of age and 10% are <40 years of age. The incidence is the same in males and females.

Diagnostic criteria

The *JAK2* V617F mutation is found in 95% of WHO defined PV, and a further 2 to 4% of patients harbour mutations in exon 12. In patients with erythrocytosis without either of these mutations, secondary or other causes of erythrocytosis should be sought.

Revised WHO diagnostic criteria (2016) for polycythaemia vera

Diagnosis requires all 3 major criteria or the first 2 major criteria and the minor criterion*

MAJOR

(i) Haemoglobin >16.5g/dl in men, >16.0 g/dl in women or haematocrit >49% in men, >48% in women or increased red cell mass >25% above mean normal predicted value.

(ii) Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)

(iii) Presence of *JAK2* V617F mutation or *JAK2* exon 12 mutation

MINOR

(i) serum erythropoietin level below the reference range for normal.

*Criterion number 2 (bone marrow biopsy) may not be required in cases with sustained absolute erythrocytosis: haemoglobin levels >18.5g/dL in men (haematocrit, 55.5%) or 16.6g/dL in women (haematocrit, 49.5%) if major criterion 3 and minor criterion are present. However, initial myelofibrosis (present in up to 20% of patients) can only be detected by performing a BM biopsy; this finding may predict a more rapid progression to overt myelofibrosis (post-PV MF).

Clinical and pathological features

Erythrocytosis may be an incidental finding or discovered during investigation of non-specific symptoms (e.g. pruritis often after a warm bath or shower, headache, tinnitus, blurred vision, abdominal discomfort, fatigue) or after an episode of gout. In 10 to 15% of cases, the diagnosis of PV occurs with, or shortly after a thrombotic event. A detailed history including cardiovascular risk factors, past medical history and concurrent medications is essential to provide optimal advice on lifestyle modifications. Physical examination may reveal a ruddy complexion or palpable splenomegaly (found in 25-40% of cases).

Investigations

FBC, renal and liver function tests, *JAK2* mutation. Consider performing ferritin, serum erythropoietin level, abdominal ultrasound and bone marrow aspirate, trephine biopsy and cytogenetic studies.

Patients lacking a mutation in *JAK2* should be investigated for secondary causes of polycythaemia.

Prognostic factors for risk-adapted therapy in PV

Risk factors for thrombosis

Age >60 years and prior history of thrombosis

The Efficacy and Safety of Low-dose Aspiring in Polycythaemia Vera (ECLAP) study reported that patients younger than 65 years without prior thrombosis have an incidence of thrombosis of 2.5 per 100 persons/year. Those older than 65 years or with prior thrombosis have an incidence of 5.0 x 100 persons/year. Those older than 65 years with prior thrombosis have an incidence of 10.9 x 100 persons/year.

Cardiovascular risk factors (smoking, hypertension, hypercholesterolemia, diabetes, obesity) should be corrected but are not formally considered during risk stratification.

Leukocytosis and *JAK2* mutant allele burden are also not formally considered during risk stratification.

Risk factors for disease progression

Approximately 10% of PV patients evolve into post-PV myelofibrosis (MF). MF evolution is difficult to predict. Leukocyte count >15 $x10^9$/L, *JAK2* mutant allele burden >50% and bone marrow fibrosis have all been associated with a higher risk of MF evolution.

Fewer than 5% of PV patients progress to AML.

Risk factors for survival

A prognostic model for overall survival has been developed based on age, leukocytosis and prior venous thrombosis. It separates patients into three groups with median survivals of 28, 19 and 11 years respectively (Tefferi et al., 2013).

Treatment

The aim of therapy is to reduce the risk of thrombosis and to provide symptom relief where required. There is no evidence to date for any treatment that alters the natural history of the disease.

Table 1 Criteria for risk stratification in patients with PV and risk-adapted therapy

Risk category	Risk variables	Therapy
Low	Age <60 years old without history of thrombosis	Venesection to haematocrit of ≤45%, aspirin and optimisation of cardiovascular risk factors
High	Age ≥60 years old and/or with history of thrombosis	Cytoreduction±venesection to haematocrit of ≤45%, aspirin* and optimisation of cardiovascular risk factors

* Or, depending on anticipated risk of future thrombosis, oral anticoagulation

(i) Optimisation of cardiovascular risk factors

Stop smoking, recommend exercise programme and dietary advice where appropriate, and optimal management of hypertension or diabetes where present. Consider making use of a cardiovascular disease risk assessment tool (e.g. QRISK2) and statin therapy.

(ii) Antiplatelet therapy

Aspirin 75mg OD unless contraindicated. Clopidogrel is an alternative.
The ECLAP study demonstrated that the risk of the combined end point of non-fatal myocardial infarction, non-fatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes was significantly reduced by low dose aspirin 100mg/day (relative risk 0.40, p = 0.03)

(iii) Venesection

Patients should receive venesection unless contraindicated (±concomitant fluid replacement) to maintain the haematocrit at ≤45%. The PVSG-01 study established venesection as first line therapy in PV.

(iv) Cytoreductive therapy

Cytoreductive therapy should be considered in high risk patients, those who tolerate venesection poorly, or in patients with symptomatic splenomegaly or thrombocytosis.

a. Hydroxycarbamide

Recommended first line therapy for cytoreduction. No controlled study has firmly demonstrated hydroxycarbamide as being leukaemogenic in PV.

b. Conventional or pegylated Interferon-alpha

Interferon is non-leukaemogenic and therefore all younger patients (≤40yr) should be offered a trial of therapy. However, the side effect profile leads to discontinuation in 20-40% of patients.

c. Anagrelide

May be effective in managing those PV patients with concomitant thrombocytosis but its side effect profile may be difficult for some patients to tolerate.

d. Radioactive phosphorus and intermittent lose dose busulphan can be considered with great caution in older patients intolerant or resistant to hydroxycarbamide.

e. Ruxolitinib. Although not available on the NHS, the JAK2 inhibitor ruxolitinib is effective therapy for poorly controlled PV patients, or those who are resistant to or intolerant of hydroxycarbamide. It is particularly effective for associated constitutional symptoms such as pruritis and sweats. In the RESPONSE trial there was improved haematocrit control, spleen size reduction and total symptom score by comparison with best available therapy The MAJIC trial comparing ruxolitinib to best available therapy in PV patients resistant to or intolerant of hydroxycarbamide has now completed recruitment in the UK and results are awaited.

Special situations

Splanchnic vein thrombosis (SVT)

PV is a frequent underlying cause of SVT that includes Budd-Chiari syndrome, mesenteric, splenic, or portal vein thrombosis. Up to 70% of SVT is developed prior to MPN diagnosis. The estimated prevalence of MPN in patients with Budd-Chiari syndrome and portal vein thrombosis is 30-50% and 15-30% respectively. Young women are preferentially affected. JAK2 V617F mutation is present in 50-60% of Budd-Chiari syndrome and 20-40% of portal vein thrombosis. It is important to note that the peripheral

blood count may be normal due to haemodilution (erthrocytosis is masked by an expanded volume of plasma). The bone marrow biopsy may not be pathognomonic.

Management should be joint with an expert hepatologist. Lifelong anticoagulation should be considered, although its risks need to be weighed in the presence of portal hypertension and oesophageal varices. Cytoreductive therapy to normalise the full blood count is recommended. Surgical treatment includes transjugular intrahepatic portosystemic shunt, angioplasty with or without stenting, surgical shunts, and liver transplantation.

Pruritis

No reliably effective therapies are currently available on the NHS. Antihistamines are often ineffective. In selected cases, phototherapy using psoralen and ultraviolet A light may be successful, as may interferon. Ruxolitinib is generally very effective if available.

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2. Essential thrombocythaemia

Muhammad Saif & Rachel Brown

Essential thrombocythemia (ET) is a clonal myeloproliferative neoplasm characterised by thrombocytosis, megakaryocytic hyperplasia, absence of the Philadelphia chromosome and no evidence of other myeloid disorders such as polycythemia vera or primary myelofibrosis. Mutations in JAK2 (V617F), CALR or MPL (W515K/L) may be found in approximately 50%, 30% and 5% of patients respectively. Recent data suggest that these molecular abnormalities may be associated with distinct clinical characteristics and may also have prognostic significance.

Diagnostic criteria

The British Committee for Standards in Haematology has provided diagnostic criteria for ET modified from the WHO criteria. These have recently been updated to incorporate CALR mutation analysis.

To diagnose ET there is a requirement to demonstrate either A1-A3 or A1 + A3–A5:

A1 Sustained platelet count >450 × 10^9/l
A2 Presence of an acquired pathogenetic mutation (e.g. in the JAK2, MPL or CALR 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)

Clinical presentation and pathological features

The median age of presentation is 60 years and thrombosis is the most common complication. Advanced age and prior history of thrombosis are the strongest predictors for future thrombosis. Other factors, such as hypertension, diabetes, dyslipidemia, smoking, leucocytosis and thrombophilia may also increase the risk of thrombosis. The correlation between thrombocytosis level and risk of future thrombosis is less clear. Indeed high platelet count may be associated with bleeding due to acquired von Willebrand Disease.

Investigations

FBC, renal and liver function tests, ferritin, *JAK2* mutation. If *JAK2* mutation negative, consider performing *CALR* or *MPL* mutation analysis. Consider bone marrow aspirate, trephine biopsy and cytogenetic studies.

Risk Stratification

As per the European Leukemia Network recommendations and BCSH guidelines, patients may be risk stratified as follows:

HIGH RISK

≥60 years of age
OR have had an ET-related thrombotic or haemorrhagic event
OR who have a platelet count of >1500 × 10^9/l

Additional high risk features include: any history of ischemia, thrombosis or embolic events, microvascular abnormalities (e.g. erythromelalgia), presence of hypertension or diabetes.

LOW RISK

<40 years of age with no high risk features

INTERMEDIATE RISK

40–60 years with no high risk features

Management

Modification of risk factors

All patients should be screened for risk factors for thrombosis such as hyperlipidemia, diabetes, hypertension and smoking and managed appropriately. Consider making use of a cardiovascular disease risk assessment tool (e.g. QRISK2) and statin therapy.

Antiplatelet therapy

Aspirin reduces the incidence of cardiovascular and thrombotic events and is recommended in all patients with ET unless contraindicated. Clopidogrel is an alternative in patients allergic to aspirin or those with peptic ulcer disease.

Indications for cytoreductive therapy

High risk patients should be offered cytoreduction aiming to reduce the platelet count to the normal range. Low and intermediate risk patients can be observed (on aspirin) and considered for cytoreductive therapy where high risk features develop.

In patients who are refractory to or intolerant of cytoreductive therapy, consider relaxing the platelet target to <600x10^9/L or change medication.

Hydroxycarbamide

Hydroxycarbamide reduces thrombotic risk in high risk ET patients and is first line therapy for most high risk ET patients. Younger patients (e.g. ≤40 years) should be offered a trial of interferon therapy.

Anagrelide

Anagrelide is an option for second line therapy in hydroxycarbamide resistant or intolerant patients. Combination treatment with hydroxycarbamide and anagrelide has also been successfully used. Anagrelide provides inferior thrombosis risk reduction compared with hydroxycarbamide. For those patients taking anagrelide monitoring by bone marrow examination every 2-3 years is essential to rule out the development of marrow fibrosis, a recognized side effect of anagrelide therapy.

Interferon alpha

Interferon is effective in reducing the platelet count in ET as well as *JAK2* allelic burden. However, there is no prospective study proving its efficacy in preventing the thrombotic complications of ET.

Younger patients (e.g. ≤40 years), or those contemplating pregnancy, should be offered a trial of interferon therapy. It can be difficult to tolerate due to its side effects and in various trials about 30% of patients discontinued its use due to intolerance. The toxicity profile of pegylated interferon is not necessarily superior to recombinant interferon but it is more convenient to administer.

Other agents

Busulphan and radioactive phosphorus are effective cytoreductive treatment options. However, both significantly increase the risk of leukaemic transformation and so should only be considered in elderly patients with no other treatment options.

JAK2 inhibitors
Ruxolitinib has been recently evaluated in clinical trials in ET but results from the MAJIC study demonstrated it was not superior to best available therapy in patients resistant to or intolerant of hydroxycarbamide. It is not available on the NHS for this indication.

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3. Myelofibrosis — Tim Somervaille

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 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.

Diagnostic criteria (World Health Organisation 2016)

Diagnosis requires all three major and at least 1 minor criterion:

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 Grades 2 or 3; 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 Essential Thrombocythaemia, 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 *CALR* mutation[a]; 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: (confirmed in 2 consecutive determinations)

(i) Leucoerythroblastosis

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

(iii) Anaemia not attributed to a comorbid condition

(iv) Leukocytosis ≥11x10^{9}/L

(v) Palpable splenomegaly

[a] *In the absence of the 3 major clonal mutations, the search for the most frequent accompanying mutations (e.g. ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1) are of help in determining the clonal nature of the disease.*
*** 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.

Diagnostic criteria for post-polycythaemia myelofibrosis

REQUIRED

(i) Documentation of a previous diagnosis of PV (see section 1 above)

(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

Post-essential thrombocythaemia myelofibrosis

ET is typically an indolent disorder characterised by long symptom-free periods interrupted by occasional haemorrhage or thrombosis. 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 (section 1 above)

(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

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

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

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

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

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. Emerging data suggest treatment with JAK2 inhibitors may provide a survival benefit.

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:

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.

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 and elsewhere 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.

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. Patients 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 evidence for a survival benefit for ruxolitinib treated patients over placebo treated patients in COMFORT-1.

Following NICE approval, ruxolitinib is available on the NHS for the treatment of symptomatic intermediate-2 or high risk primary myelofibrosis (or post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis). It is of particular value in patients with constitutional symptoms of disease or pruritus. Patients with single disease-related issues such as isolated uncomfortable splenomegaly or anaemia will likely benefit from alternative therapeutic approaches.

In view of its expense, ruxolitinib should only be prescribed where the anticipated benefits clearly outweigh the benefits to be gained from alternative therapies (se Management of Specific Issues section, below).

Other JAK2 inhibitors have not been so successful in clinical trials, but continue under some form of clinical investigation (October 2017) i.e. pacritinib and momelotinib. It remains unclear whether either will make it to market. Pacritinib may benefit patients with myelofibrosis who have significant thrombocytopaenia. Momelotinib may benefit patients who have significant anaemia.

This is a fast-moving area of research and recommendations may continue to change over ensuing months and years. However, it seems likely that the majority of symptomatic intermediate-2 and high risk patients benefit (and possibly with prolonged survival) through treatment with a JAK2 inhibitor.

Where possible, patients should be considered for referral for clinical trials in view of the rarity of this disease and the generally poor outcomes.

Given that there have been infrequent reports of reactivation of latent and atypical infections in patients taking ruxolitinib (e.g. hepatitis B and tuberculosis), the prescriber should consider screening for these and consider use of appropriate prophylactic measures (e.g. aciclovir prophylaxis). Live vaccinations should be also be considered with caution.

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 in the absence of significant cytopaenias can be treated with anti-proliferative chemotherapy such as hydroxycarbamide (or ruxolitinib in the presence of concomitant constitutional symptoms). 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. 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 a trial of erythropoietin or darbopoietin is recommended. Erythropoiesis stimulating agents can exacerbate spleen size in those with significant splenomegaly, so caution is advised under these circumstances.

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 regularly with a liver USS every 6-12 months. Male patients should be screened for prostate cancer (i.e. PSA) 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 including pruritis

These are best managed with a JAK2 inhibitor.

Minimising thrombotic risk

For patients with a platelet count >450x10^9/l, there is likely an increased thrombotic risk. Here treatment with hydroxycarbamide (or a JAK2 inhibitor where concomitant constitutional symptoms are present) 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). Consider making use of a cardiovascular disease risk assessment tool (e.g. QRISK2) and statin therapy.

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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