bjh guideline

Guideline for the diagnosis and management of myelofibrosis

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Summary

The guideline group regarding the diagnosis and management of myelofibrosis was selected to be representative of UK-based medical experts, together with a contribution from a single expert from the USA. MEDLINE and EMBASE were searched systematically for publications in English from 1966 until August 2011 using a variety of key words. The writing group produced the draft guideline, which was subsequently revised by consensus of the members of the General Haematology and Haemato-oncology Task Forces of the British Committee for Standards in Haematology (BCSH). The guideline was then reviewed by a sounding board of UK haematologists, the BCSH and the British Society for Haematology Committee and comments incorporated where appropriate. The criteria used to state levels and grades of evidence are as outlined in the Procedure for Guidelines commissioned by the BCSH; the 'GRADE' system was used to score strength and quality of evidence. The objective of this guideline is to provide healthcare professionals with clear guidance on the investigation and management of primary myelofibrosis, as well as post-polycythaemic myelofibrosis (post-PV MF) and post-thrombocythemic myelofibrosis (post-ET MF) in both adult and paediatric patients.

Keywords: myelofibrosis, myeloproliferative disorders, transplantation, treatment.

Aim

The purpose of this guideline is to provide a practical, rather than a research, approach to the diagnosis, investigation and management of patients with primary, as well as post-polycythaemic myelofibrosis (post-PV MF) and post-thrombocythemic myelofibrosis (post-ET MF). The criteria used to state levels and grades of evidence are as outlined in the Procedure for Guidelines commissioned by the BCSH; the 'GRADE' system was used to score strength and quality of evidence (Table I).

Clinical features

Myeloproliferative myelofibrosis can present as a *de novo* disorder (PMF) or evolve secondarily from previous polycythaemia vera or essential thrombocythaemia (Post-PV MF or Post-ET MF respectively); the term myeloproliferative neoplasm (MPN)-associated myelofibrosis has been suggested to encompass all of these entities. Regardless of whether myelofibrosis is primary or secondary, the disease is characterized by a clonal haemopoietic stem cell proliferation associated with a characteristic stromal pattern, a leuco-erythroblastic blood film and elevated levels of various inflammatory and pro-angiogenic cytokines.

The clinical features of myelofibrosis are variable and include progressive anaemia, leucopenia or leucocytosis, thrombocytopenia or thrombocytosis and multi-organ extramedullary haemopoiesis, most commonly causing hepatomegaly and symptomatic splenomegaly. Patients with advanced disease experience severe constitutional symptoms, the consequences of massive splenomegaly (pain, early satiety, splenic infarction, portal hypertension and dyspnoea), progressive marrow failure, pulmonary hypertension, transformation to leukaemia and early death.

Diagnosis

The diagnosis of PMF, as defined by the World Health Organization (WHO; Thiele *et al*, 2008), is based on a

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Table I. Evidence statements and grades of recommendations.

Strength of recommendations
Strong (*grade 1*)*:* Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.
Weak (*grade 2*)*:* Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.
Quality of evidence
The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what we know or our certainty.
(*A*) *High:* Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomized clinical trials without important limitations.
(*B*) *Moderate:* Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomized clinical trials with important limitations (e.g. inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g. lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g. large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).
(*C*) *Low*: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

combination of clinical, morphological, cytogenetic and molecular features. Furthermore, the diagnoses of Post-PV MF and Post-ET MF have recently been clarified by the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) with the criteria being adopted by the WHO (Barosi *et al*, 2008). However, the robustness and utility of these criteria have been questioned. For example, key diagnostic difficulties may arise in differentiating a myelodysplastic syndrome (MDS) with fibrosis from PMF and between ET and some early forms of PMF (Wilkins *et al*, 2008; Beer *et al*, 2010, 2011). Furthermore, a raised lactate dehydrogenase level has recently been shown to lack specificity for primary myelofibrosis (Beer *et al*, 2010). In view of these limitations, it is recommended that the diagnostic criteria proposed by Campbell and Green (2006) for PMF (Table II), as well as for Post-PV MF and Post-ET MF (Table III) be adopted.

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

A1	Bone marrow fibrosis ≥ 3 (on 0–4 scale).
A2	Pathogenetic mutation (e.g. in *JAK2* or *MPL*), or absence of both *BCR-ABL1* 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

*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.

A1	Bone marrow fibrosis ≥ 3 (on 0–4 scale)
A2	Previous diagnosis of ET or PV
B1	New palpable splenomegaly or increase in spleen size of ≥ 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.

*Drenching night sweats, weight loss >10% over 6 months, unexplained fever (>37·5°C) or diffuse bone pains.

Molecular investigations

JAK2

Mutational screening should be carried out routinely in patients with PMF, as the *JAK2 V617F* mutation is present in approximately 45–68% of cases (Tefferi *et al*, 2005, 2008; Campbell *et al*, 2006; Barosi *et al*, 2007; Guglielmelli *et al*, 2009). While a high *JAK2* V617F allele burden, is associated with a higher transformation rate to MF in both PV and ET (Vannucchi *et al*, 2007; Passamonti *et al*, 2010a), quantitative assays are currently of no value in determining therapy for MPN patients.

BCR-ABL1

Presence of *BCR-ABL1* rearrangement (diagnostic of chronic myeloid leukaemia) excludes PMF and testing should be performed if atypical features are present on the trephine biopsy, or if the patient lacks a mutation in *JAK2* or *MPL*.

Other mutations

MPL W515L mutations were first described in 4/45 (9%) cases of *JAK2* V617F mutation-negative PMF (Pikman *et al*,

2006), an incidence confirmed by other studies (Pardanani *et al*, 2006; Guglielmelli *et al*, 2007). *MPL* mutation-positive patients were older, more frequently female and presented with more severe anaemia (Guglielmelli *et al*, 2007). Testing for *MPL* exon 10 mutations can be considered in cases that are negative for *JAK2* V617F. Mutations in *TET* oncogene family member 2 (*TET2*) occur in approximately 15% of cases of PMF and are associated with older age and anaemia but there is no correlation with overall survival (OS) or risk of leukaemic transformation (Tefferi *et al*, 2009a) and *TET2* testing is not recommended on a routine basis. The clinical significance of mutations in other genes, including *IDH1, IDH2, ASXL1, SH2B3, IKZF1, CBL* and *NRAS*, remain unclear. *EZH2* mutations are seen in about 5% of cases and have been associated with a poor prognosis (Guglielmelli *et al*, 2011), but routine screening of this large gene is not warranted at present.

PDGFRA and *PDGFRB* rearrangements, however, should be excluded in the presence of significant eosinophilia, as *PDGFRA/B*-rearranged MPNs are highly sensitive to imatinib therapy.

Recommendations

- ***JAK2* V617F mutation screening should be carried out routinely in patients with PMF. Quantitative results are not required for clinical management.**
- ***BCR-ABL1* rearrangemzent should be excluded in cases with atypical trephine biopsy features, or if the patient lacks a mutation in *JAK2* or *MPL*.**
- ***PDGFRA* and *PDGFRB* rearrangements should be excluded in the presence of significant eosinophilia (Screening for other mutations remains a research tool and routine screening cannot be justified, apart from in cases of diagnostic difficulty where detection of a clonal abnormality would be informative) (Evidence level 2, Grade B).**

Prognosis

Therapeutic decision-making in PMF, especially determining the need for allogeneic stem cell transplantation (allo-SCT) requires an accurate assessment of an individual patient's prognosis. Until recently, the most widely used prognostic system has been the so-called Lille Score (Dupriez *et al*, 1996). To address deficiencies with the latter, Cervantes *et al* (2009) published the International Prognostic Scoring System (IPSS), based on the analysis of 1054 patients, which estimates survival from the time of diagnosis, based on five risk factors: age >65 years, haemoglobin concentration <100 g/l, leucocyte count >25 $\times$ 10^9/l, circulating blasts $\geq$1% and the presence of constitutional symptoms. Based on the presence of 0 (low risk), 1 (intermediate risk-1), 2 (intermediate risk-2) or 3 or more (high risk) of these variables, four risk groups were identified, with no overlap in survival curves, with median survivals of 135, 95, 48 and 27 months, respectively (Table IV).

Using the same five prognostic variables, Passamonti *et al* (2010b) subsequently modified the IPSS for use at any time during the disease course, producing the so-called Dynamic IPSS (DIPSS; Table IV). A further refinement, DIPSS Plus, (Gangat *et al*, 2011) shows that the addition of three additional independent risk factors, transfusion dependence,

Table IV. Prognostic criteria.

Variable	IPSS	DIPSS
Age > 65 years	✓	✓
Constitutional symptoms	✓	✓
Haemoglobin <100 g/l	✓	✓
Leucocyte count > 25 $\times$ 10^9/l	✓	✓
Circulating blasts $\geq$1%	✓	✓
	1 point each	1 point each but Hb = 2

DIPSS-Plus: add 1 point to the DIPSS RISK GROUP* (low = 0; intermediate 1 = 1, intermediate 2 = 2 and high risk = 3) in addition for:
Platelet count <100 $\times$ 10^9/l
RBC transfusion need
Unfavourable karyotype +8, −7/7q−,i(17q),inv(3), −5/5q−, 12p−, 11q23 rearrangement

	IPSS		DIPSS		DIPSS-Plus	
Risk group	Predictors (*n*)	Median survival (years)	Predictors (*n*)	Median survival (years)	Predictors (*n*)	Median survival (years)
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	2	4·0	3 or 4	4	2–3	2·9
High	$\geq$3	2·3	5 or 6	1·5	$\geq$4	1·3

*Note that this is the risk group NOT the sum of points.

unfavourable karyotype (including +8, −7/7q−, i(17q), inv (3), −5/5q−, 12p−. 11q23 rearrangements and complex karyotypes) and platelet count $<100 \times 10^9$/l, gives the four prognostic groups an even greater discrimination, with corresponding median survival estimates of 185, 78, 35 and 16 months (Table IV). Although a number of molecular findings have been shown to adversely affect prognosis, including low *JAK2* V617F allele burden (Guglielmelli *et al*, 2009) and *EZH2* mutational status (Guglielmelli *et al*, 2011), such parameters have not yet been incorporated into practical prognostic scoring systems, although the findings suggest that future improvements are likely.

Recommendation

- **Therapeutic decisions in PMF, especially regarding the use of allo-SCT, should be based on the patient prognosis as determined by the DIPSS Plus as this is validated for any timepoint of the disease and is more discriminating in median survival prediction than the IPSS score.**
- **Whilst the IPSS, DIPSS and DIPSS Plus have not been validated for post-PV MF and post-ET MF, it is suggested that they still be used in this setting (Evidence level 2, Grade B).**

Treatment

Splenomegaly and extramedullary haemopoiesis

Medical treatment remains the treatment of choice for most patients with symptomatic splenomegaly. However, no current therapies deliver robust sustained responses, particularly for patients with massive splenomegaly:

Hydroxycarbamide. This is the most widely used agent, despite limited published data supporting its efficacy. An early study suggested a response rate of approximately 45% (Löfvenberg & Wahlin, 1988), although the degree of splenic reduction was not detailed. Similar findings were reported in a recent study of 18 MPN patients with symptomatic splenomegaly (Martinez-Trillos *et al*, 2010). Overall, complete responses are rare and doses of more than 1·5 g/d may be required to achieve clinical effect. Benefit is usually seen within 8–10 weeks of treatment, although side effects, especially significant cytopenias, may be problematic at effective doses.

An Italian study investigated the efficacy of low-dose melphalan (2·5 mg/thrice weekly) in PMF and documented a similar response rate to that shown in the hydroxycarbamide studies highlighted above, although with the added information that normalization of spleen size was achieved in only 4·5% in patients with massive splenomegaly ($\geq$15 cm; Petti *et al*, 2002). Furthermore, there was no survival benefit in those that responded. Bulsulphan may also produce clinical benefit (Manoharan & Pitney, 1984; Chang & Gross, 1988), but myelosuppression and an increased risk of acute leukaemia are potential adverse factors.

Immunomodulatory agents. Immunomodulatory drugs have been evaluated in a number of small studies. Low-dose thalidomide (50 mg/d), for example, combined with a tapering dose of prednisolone resulted in an overall response rate of 33% (Mesa *et al*, 2003), although subsequent follow-up data showed that only 8% of patients obtained a clinical improvement in splenomegaly (Thapaliya *et al*, 2011), as defined by the more stringent IWG-MRT criteria (Tefferi *et al*, 2006a). Responses were also reported for anaemia (22%) and thrombocytopenia (50%). Lenalidomide has also been shown to produce a response rate of 33% in a study that included some patients who had failed on prior thalidomide therapy (Tefferi *et al*, 2006b).

Interferon-alpha. Both standard and pegylated preparations of interferon-alpha appear to have little clinical effect in reducing splenomegaly and, as a result, their use is not recommended (Tefferi *et al*, 2001a; Jabbour *et al*, 2007; Ianotto *et al*, 2009). They do, however, have a role as myelosuppressive agents (see 'Myelosuppression Therapy' section).

Cladribine. This purine analogue, previously known as 2-chlorodeoxyadenosine, has been shown to reduce clinically significant post-splenectomy hepatomegaly and post-splenectomy thrombocytosis in 56% and 50% of patients respectively, although myelosuppression is a significant side-effect. The drug, which can be administered for up to 4 monthly cycles, frequently resulted in durable responses, which lasted for a median of 6 months after discontinuation of therapy (Faoro *et al*, 2005).

JAK inhibitors. JAK inhibitors may have a future role in the management of splenomegaly (see 'Novel Therapies' section) and are the only therapies to have been evaluated in the context of randomized clinical trials.

Recommendations: medical management of splenomegaly

First Line:

- Hydroxycarbamide (in the absence of cytopenias).
- Thalidomide and prednisolone (in presence of cytopenias) – consider lenalidomide (if anaemic with platelet count $>100 \times 10^9$/l).

Second Line:

- Consideration should be given to the use of JAK inhibitors either as part of a clinical trial, or via patient access protocols. These agents are now approved in the USA for first line therapy which is appropriate following approval (Evidence level 1, Grade A).

Surgical management

The place of splenectomy in the management of myelofibrosis is well established (Barosi *et al*, 1993; Tefferi *et al*, 2000). Routine splenectomy is inappropriate and the procedure should be restricted to carefully selected patients with refractory haemolysis, symptomatic splenomegaly, significant splenic infarction, severe portal hypertension and severe hypercatabolic symptoms. Once a patient is considered a candidate for splenectomy, an extensive pre-operative evaluation is required to determine if the cardiac, hepatic, renal, metabolic and haemostatic risks are acceptable. Even in the best units, splenectomy is associated with morbidity and mortality rates of approximately 31% and 9%, respectively (Tefferi *et al*, 2000). Laparoscopic splenectomy is not advised in PMF on account of bleeding complications (Feldman *et al*, 2008). Splenic artery embolization is not without risk and there is no evidence to support its use.

Patients with portal hypertension and bleeding varices should have dynamic circulatory studies performed during surgery, because portal hypertension due to splenomegaly is ameliorated by splenectomy, in contrast to cases secondary to intra-hepatic obstruction, which require a portal-systemic shunt. Transjugular intrahepatic portosystemic shunt (TIPS) appears a reasonable treatment modality for intrahepatic obstruction, based on the results from several case-reports (Angermayr *et al*, 2002; Wiest *et al*, 2004; Alvarez-Larran *et al*, 2005; Doki *et al*, 2007).

Hepatic extramedullary haematopoiesis leading to rapid hepatic enlargement is an unusual but well recognized complication and unexpectedly high rates of leukaemic transformation have been documented (López-Guillermo *et al*, 1991; Barosi *et al*, 1998); the latter finding is believed to relate to patient selection, rather than a true alteration in the disease biology, as there is no reason to believe disease biology, related to clonal stem cell abnormality, would be altered by splenectomy. Importantly, a significant post-operative thrombocytosis is observed in approximately 20% of patients and carries an increased thrombotic risk (Barosi *et al*, 1993). It is for this reason that normalization of platelet counts pre- and post-splenectomy is strongly recommended. Furthermore, cladribine may be considered as a palliative option for patients with post-splenectomy myeloproliferation that is refractory to hydroxycarbamide (Faoro *et al*, 2005).

Recommendations for splenectomy

Indications

- Drug-refractory symptomatic splenomegaly.
- Drug-refractory anaemia.
- Symptomatic portal hypertension (e.g. ascites, bleeding varices).
- Severe catabolic symptoms including cachexia (Evidence level 2, Grade C).

Peri-operative management

- Evaluate cardiac, hepatic, renal and metabolic status.
- Correction of any coagulopathy.
- Meticulous control of platelet count pre- and post-splenectomy.
- Laparoscopic splenectomy not advised.
- Splenic artery embolization not advised.
- Appropriate vaccination and long-term penicillin (Evidence level 2, Grade C).

Post-splenectomy myeloproliferation

- Cytoreductive therapy (hydroxycarbamide). Cladribine can be considered in selected patients (Evidence level 2, Grade C).

Radiotherapy

Radiotherapy is a valuable alternative to splenectomy in patients with symptomatic splenomegaly and an adequate platelet count ($>50 \times 10^9$/l) and in whom surgery is deemed unsuitable. However, while symptomatic relief, with mild to moderate reduction in spleen size, occurs in the majority of cases, the response is only short lived. In the Mayo Clinic experience, a median radiation dose of 277 cGy was administered in a median of 7·5 fractions. Reduction in spleen size was noted in the majority of cases and lasted for a median of 6 months, although 44% experienced cytopenias, of which 13% were fatal (Elliot *et al*, 1998). Median survival after irradiation was 22 months. A subsequent study administered a median of 980 cGy with a response rate of 59% and a median duration of response of 10 months (Bouabdallah *et al*, 2000).

Furthermore, a case report suggested that low-dose intermittent radiation, e.g.100 cGy, every 1–3 months, might be a reasonable approach to control post-splenectomy, hepatomegaly symptoms (Riesterer *et al*, 2008). The optimal radiation dose and schedule has not been determined, but caution should be exercised in cytopenic and/or heavily pre-treated patients. In these cases starting with a low dose (≤ 50 cGy) once or twice weekly with blood count monitoring would be recommended as the individual sensitivity is variable and cannot be predicted.

The use of splenic irradiation does not preclude subsequent splenectomy. There is a suggestion, however, that operative mortality in this setting is increased, although this is based on only nine patients in the Mayo series, of which a third developed post-operative intra-abdominal haemorrhage necessitating surgical exploration, with one death. The transient response, together with the operative mortality rates for patients requiring subsequent splenectomy, suggests that radiotherapy should not be regarded as an alternative to splenectomy in surgical candidates. Re-irradiation is usually possible as long as kidney tolerance doses are not exceeded.

Low-dose irradiation remains the treatment of choice for extramedullary haematopoiesis (EMH) at other sites,

including involvement of the peritoneum and pleura with resultant ascites and pleural effusions, respectively (Leinweber *et al*, 1991; Kupferschmid *et al*, 1993; Bartlett *et al*, 1995). External beam radiotherapy is also effective for the involvement of vital organs, including the lung, central nervous system and liver (Price & Bell, 1985; Landolfi *et al*, 1988; Tefferi *et al*, 2001b; Steensma *et al*, 2002). Recently, low-dose radiation has also been shown to be an effective therapy for severe extremity pain (Neben-Wittich *et al*, 2010). Five patients received 10–60 cGy in a single fraction with three cases experiencing complete and one partial resolution of pain with no reported side effects.

Recommendations

Radiotherapy for:

- **Patients with symptomatic splenomegaly, who have an adequate platelet count (>50 × 10^9/l) and who are not deemed suitable for surgical intervention. Platelet transfusions may be required post-treatment.**
- **EMH involving vital organs.**
- **Severe bone pain (Evidence level 2, Grade C).**

Treatment of anaemia

Blood transfusion

As with most clinical scenarios, the efficacy of blood transfusion in PMF has not been proven, nor has its efficacy been subjected to evaluation by a randomized trial. Nevertheless, blood transfusion is standard therapy for symptomatic patients and should be assessed individually.

Regular transfusions will eventually lead to iron overload, although it remains unclear whether this leads to toxicity and end-organ damage. Indeed, hyperferritinaemia has not been shown to affect survival in patients with PMF (Tefferi *et al*, 2009b). As a result, chelation therapy is not routinely recommended. This may not be true for patients receiving an allogeneic transplant, where improved survival was observed in patients who had received <20 units of red blood cells (see Transplant recommendation section).

Transfusion recommendations

- Red cell transfusions are recommended in PMF patients with symptomatic anaemia (Evidence level 2, Grade B).
- Iron chelation therapy is not routinely recommended in PMF (Evidence level 2, Grade B).

Erythropoietin

The efficacy of recombinant human erythropoietin (rEPO) appears to be limited principally to a subgroup of patients with inappropriately low endogenous EPO levels in the face of relatively moderate anaemia. The reported experience with rEPO in PMF has generally been limited to small case series, the interpretation of which is confounded by non-uniform response criteria, varying rEPO dosing regimens and a range of concomitant therapies.

In an analysis of 20 anaemic MF patients treated with rEPO, responses were seen in 45% of cases but only maintained long-term in 20% (Cervantes *et al*, 2004); responses to rEPO being more likely in transfusion-independent patients with higher baseline Hb. A pooled analysis of this 20-patient series with 31 patients from the literature demonstrated an overall rEPO response rate of 55% [31% complete response (CR)] with a median duration of 12 months (Cervantes *et al*, 2004). Multivariate analysis showed that an inappropriately low baseline serum EPO level (<125 u/l) was associated with favourable response to rEPO. The most described starting dose of rEPO is 10 000 units three times weekly, this being doubled after 1–2 months in cases where no early response is seen.

The published experience with darbepoietin, a hyperglycosylated erythropoietin derivative that can be administered less frequently, remains limited to a single case series (Cervantes *et al*, 2006a). Twenty anaemic MF patients received darbepoietin at an initial weekly dose of 150 μg, increasing to 300 μg after 4–8 weeks in the absence of an early response. Responses were seen in 40% (30% CR) with five responses being maintained at 5 months. Responses to darbepoietin were seen in both transfused and transfused-independent cases, but only in those individuals with baseline EPO levels of <125 u/l.

Recommendations for erythropoietin

- **A trial of recombinant erythropoietin therapy should be considered in anaemic PMF patients with inappropriately low erythropoietin levels (<125 u/l). Responses are more likely in those with relatively moderate anaemia (Evidence level 2, grade B).**
- **rEPO should be commenced at a dose of 10 000 units three times weekly (or darbepoietin 150 μg weekly), doubling to 20 000 three times weekly (darbepoietin 300 μg weekly) after 1–2 months in the absence of an early response. Treatment should be discontinued after 3–4 months if no response occurs (Evidence level 2, grade B).**

Androgens

The effect of androgens on erythropoiesis has been recognized for over half a century and this topic has been recently reviewed (Shahani *et al*, 2009). A number of androgens have been trialled including nandrolone (Gardner & Besa, 1977; Besa *et al*, 1982), testosterone (Silver *et al*, 1964; Gardner & Besa, 1977; Besa

et al, 1982), fluoxymesterone (Gardner & Besa, 1977; Brubaker *et al*, 1982), oxymethalone (Alexanian *et al*, 1972; Gardner & Besa, 1977; Hast *et al*, 1978), etiocholanolone (Gardner & Besa, 1977) and danazol (Levy *et al*, 1996; Cervantes *et al*, 2000, 2005). Response rates to androgen therapy are reported as varying, most frequently between 30% and 60%. It is interesting to note that the failure of one androgen to improve anaemia does not necessarily predict the response to another (Gardner & Besa, 1977).

Danazol, a synthetic attenuated androgen, has found increasing favour as the first line androgen of choice in myelofibrosis. This agent has been shown to have the additional benefits of reducing spleen size in a proportion of patients (Levy *et al*, 1996) and improving platelet counts (Cervantes *et al*, 2000). In the updated study by Cervantes *et al* (2005), patients were initially commenced on danazol at a dose dependent on body weight: 600 mg daily for those weighing up to 80 kg and 800 mg daily for those with a body weight >80 kg. This dose was continued for a minimum period of 6 months before evaluating response. Those achieving a favourable response were maintained on danazol at a reduced dose of 400 mg daily for a further 6 months before the dose was titrated down to the minimum required to maintain a response (200 mg daily).

Although androgen side effects are well recognized including fluid retention, increased libido, hirsutism, deranged liver function tests (LFTs) and hepatic tumours, only two responders in the study by Cervantes *et al* (2005) discontinued treatment because of toxicity (one from cholestatic hepatitis and one from prostatic adenocarcinoma). Based on these observations, Cervantes *et al* (2005) recommended that all patients receiving danazol have LFTs monitored at least monthly during initial therapy and liver ultrasound for hepatic malignancy every 6–12 months. They also recommend males should be screened for prostate cancer before therapy and during treatment.

Recommendations for androgens

- **Danazol should be considered as a therapeutic option to improve the haemoglobin concentration of patients with myelofibrosis and transfusion-dependent anaemia (Evidence level 2, Grade B).**
- **Recommended starting dose is 200 mg daily, with a gradual dose escalation, depending on tolerability and patient weight (to a maximum of 600 mg daily for patients <80 kg and 800 mg for patients >80 kg) (Evidence level 2, Grade B).**
- **Patients should be treated for a minimum period of 6 months. Responding patients should be maintained for a further 6 months on 400 mg daily before titrating down the dose to the minimum required to maintain a response (Evidence level 2, Grade B).**
- **LFTs should be monitored at least monthly initially and liver ultrasound is recommended every 6–12 months to exclude hepatic malignancy (Evidence level 2, Grade C).**
- **Male patients should be screened for prostate cancer before and during therapy (Evidence level 2, Grade B).**

Management of constitutional symptoms

Multiple symptoms, such as fatigue, weakness, abdominal pain, cachexia, weight loss, pruritus, night sweats and bone pain are common in patients with PMF, particularly, but not exclusively, in those with advanced disease. The debilitating symptoms of myelofibrosis are thought to be driven by the combined effects of massive splenomegaly and elevated levels of proinflammatory cytokines. Quality of life scores for PMF patients have been reported to be equivalent to those for advanced metastatic cancer (Scherber *et al*, 2011). The efficacy of conventional therapy in moderating these symptoms is poor. Evidence for major benefit of JAK inhibitors is accruing in this area, thus far however this has been tested for patients with the combination of splenomegaly and constitutional symptoms.

Recommendations for constitutional symptoms

Management of consitutional symptoms in PMF is challenging and there is no evidence of benefit for conventional agents in this area. Patients with profound symptoms are usually in the poor risk group and should be considered for experimental therapy wih JAK inhibition (Evidence level 1, Grade A).

Myelosuppressive therapy

Myelosuppressive therapy in PMF is not curative and there are relatively few published series, most of which are small, non-randomized and incorporate different definitions of response. Nevertheless, indications for myelosuppression include the control of symptoms related to hypercatabolism (fever, night sweats, fatigue, weight loss, bone pains), splenomegaly and hepatomegaly, as well as reducing an associated leucocytosis and/or thrombocytosis. Indeed, the role of thrombocytosis in contributing to the increased thrombotic risk in PMF patients has been highlighted by a Spanish study (Cervantes *et al*, 2006b). It was shown on multivariate analysis that thrombotic risk is linked to thrombocytosis (platelets $>450 \times 10^9$/l) and the cellular phase of the disease, as well as to the presence of cardiovascular risk factors (arterial hypertension, smoking, hypercholesterolaemia or diabetes). As a result, we recommend that such patients should be treated according to the British Committee for Standards in Haematology (BCSH) guidelines for the management of thrombocytosis (Harrison *et al*, 2010). A number of agents can be used:

Hydroxycarbamide

Recently, Martinez-Trillos *et al* (2010) have reported that hydroxycarbamide is an effective and relatively well-tolerated therapy for the control of the hyperproliferative symptoms of PMF. Anaemia, however, can be aggravated and is usually manageable with the addition of erythropoietin. To be labelled as being resistant to hydroxycarbamide, one of the following criteria should be fulfilled: failure of improvement in organomegaly by 50%, failure of complete resolution of symptoms related to organomegaly, uncontrolled myeloproliferation despite receiving at least 2 g/d for 3 months and cytopenias at the lowest dose of hydroxycarbamide required to achieve respone (Barosi *et al*, 2010).

Anagrelide

Data from the Primary Thrombocythaemia 1 study (Harrison *et al*, 2005) and the Swedish Myeloproliferative Disorder Study Group (Hultdin *et al*, 2007)have suggested that anagrelide treatment, when compared with hydroxycarbamide, may be associated with an increase in reticulin grade. As a consequence, the BCSH guidelines for the investigation and management of patients presenting with thrombocytosis suggest regular monitoring for development of MF in patients treated with this agent and a change of therapy should this occur (Harrison *et al*, 2010). For patients with an establish PMF, there is no published evidence to suggest anagrelide therapy is associated with disease progression although this has not been tested in a robust manner. A recommendation to treat with caution is made.

α-interferon (IFN-α)

Despite a strong preclinical rationale for the use of conventional IFN-α in MF patients (Kiladjian *et al*, 2008), objective response rates in early clinical studies were disappointing. In view of the particularly high rates of toxicity in PMF, the use of IFN in MPNs has been mainly restricted to PV and ET. Nevertheless, a number of studies of IFN in MF have been reported, although they give highly heterogeneous results, a fact complicated by non-standardized reporting of responses and lack of randomized control trial data (Gilbert, 1998; Tefferi *et al*, 2001a; Radin *et al*, 2003; Jabbour *et al*, 2007; Ianotto *et al*, 2009; Silver & Vandris, 2009). More recently, two small, retrospective, observational studies have shown more promising results in PMF patients. First, a group from Cornell University reported that the use of IFN-α2b early in the disease course, starting at a very low dose (0·5–1·0 million units three times per week), can retard disease progression, with some patients exhibiting regression of marrow fibrosis (Silver & Vandris, 2009). A second study observed clinically significant efficacy of pegylated-IFN-α2a in PMF, with 44% of patients experiencing complete or major responses, with six of eight patients normalizing haemoglobin levels (including two of three transfusion-dependent patients; Ianotto *et al*, 2009). In both studies, patients with advanced disease and massive splenomegaly showed a lower response rate. In contrast, IFN demonstrated particular efficacy in patients with proliferative patterns of disease, with either leucocytosis or thrombocytosis. It is also noteworthy that IFN-α has shown some efficacy in the treatment of transformed myelofibrosis (Berneman *et al*, 2010).

Recommendations for myelosuppressive therapy

- **Hydroxycarbamide is the first line choice for the control of the hyperproliferation manifestations of myelofibrosis (Evidence level 2, Grade B).**
- **Anagrelide should be used with caution in patients with established MF (Evidence level 2, Grade B).**
- **Use of IFN-α in PMF patients should be restricted to cases with early phase disease with more proliferative disease features (Evidence level 2, Grade B).**
- **High starting doses of conventional IFN-α are very poorly tolerated in PMF and should be avoided. When conventional IFN-α is used, it is recommended to commence at 1·5 million units three times per week and increase to a maximum of 15 million units/week as tolerated. If using pegylated-IFN, α2a is the recommended agent (Evidence level 2, Grade B).**

Bone marrow transplantation

Autologous stem cell transplant (auto-SCT)

The literature on the use of auto-SCT in PMF is sparse and is mainly based on an early pilot study (Anderson *et al*, 2001). Overall, however, this study suggested that auto-SCT conferred a modest benefit at best. A subsequent report confirmed a lack of significant therapeutic efficacy (Fruehauf *et al*, 2005). Given these findings, auto-SCT cannot be recommended in PMF (Evidence level 2, Grade C).

Allogeneic haemopoietic stem cell transplantation (allo-HSCT)

Since the initial report of successful HSCT in myelofibrosis (Dokal *et al*, 1989), multiple publications have confirmed the potentially curative effect of HSCT with stable engraftment and reversal of bone marrow fibrosis (Devine *et al*, 2002; Daly *et al*, 2003; Ditschkowski *et al*, 2004; Rondelli *et al*, 2005; Gupta *et al*, 2009; Bacigalupo *et al*, 2010; Lissandre *et al*, 2011; Samuelson *et al*, 2011). Several groups have reported survival outcomes at ≥ 3 years post-HSCT (Guardiola *et al*, 1997, 1999; Kerbauy *et al*, 2007; Patriarca *et al*, 2008; Kröger *et al*, 2009a; Bacigalupo *et al*, 2010; Ballen *et al*, 2010; Stewart *et al*, 2010; Abelsson *et al*, 2011; Nivison-Smith *et al*, 2011; Table V).

Table V. Allogeneic HSCT for myelofibrosis.

Study	Guardiola *et al* (1999)	Kerbauy *et al* (2007)	Abelsson *et al* (2011)	Patriarca *et al* (2010)	Stewart *et al* (2010)	Ballen *et al* (2010)	Kröger *et al* (2009b)	Nivison-Smith *et al* (2011)
Centre(s)/Group	Europe and USA	Seattle	Nordic countries	Italy	UK and Ireland	CIBMTR	EBMT	Australia
HSCT performed	1979–1997	>1990 (except 3)	1982–2009	1998–2006	1989–2005	1989–2002	2002–2007	1993–2005
Patients (*n*)	55	104	92	52	51	289	103	57
Age, years (range)	42 (4–53)	49 (18–70)	MA 46 (34–58) RIC 55 (47–63)	52·5 (32–68)	MA 38 (19–54) RIC 54 (40–64)	47 (18–73)	55 (32–68)	47 (16–71)
Lille score ≥ 1 (%)	38	58	MA 82 RIC 78	89	MA 76* RIC 75*	67	83	54*
MA/RIC (*n*)	55/0	95/9	40/52	–/52	27/24	229/60	–/103	40/17
TRM								
Day 100	–	13	MA 17·5; RIC 5·8	–	MA 26; RIC 21	All HLA-id Sib 18 All MUD 35	16 95% CI 19–23	18
1 year (%)	27 (21–33)	–	–	30	–	All HLA-id Sib 27 All MUD 43 RIC HLA-id 15 RIC MUD 49		25
OS								
3-year	–	–	–	44	MA 44; RIC 31			
5-year (%)	47 (39–55)	61 (95% CI 43–65)	MA 49; RIC 59	–	–	All HLA-id Sib 37 All MUD 30	67 95% CI 55–79	58
DFS								
3-year	–	–	–	38	MA 15; RIC 24	RIC HLA-id Sib 39 RIC MUD 17		
5-year (%)	39 (32–46)			–	–	All HLA-id Sib 33 All MUD 27	51 95% CI 38–64	57

CI, confidence interval; CIBMTR, Centre for International Bone Marrow Transplant Research; DFS, disease free survival; EBMT, European Group for Blood and Marrow Transplantation; HLA-id Sib, human leucocyte antigen-matched sibling; HSCT, haemopoietic stem cell transplantation; MA, myeloablative conditioning; MUD, matched unrelated donor; OS, overall survival; RIC, reduced intensity conditioning; TRM, transplant related mortality; UK, United Kingdom.

*Incomplete data.

It should be stressed, however, that there are no randomized controlled trials (RCTs) comparing allo-HSCT to any alternative/supportive therapy; nor are there any RCTs comparing myeloablative (MA) versus reduced intensity conditioning (RIC) allo-HSCT. We are reliant, therefore, on non-comparative reported series as the principal evidence base (Table V). Attempts to evaluate these are further complicated by the substantial heterogeneity of the patient populations with respect to age, prognostic groups, co-morbidities, stem cell source, donor source, conditioning protocols (MA and RIC), graft-versus-host disease (GvHD) prophylaxis, pre-transplant red cell and platelet transfusion dependency and iron loading. Patients with differing prognostic scores at the time of transplant are often included in the same series, making the outcomes difficult to evaluate against a median predicted survival in the absence of a transplant. Additionally, some of the larger published case series include transplants carried out up to 20 years ago. In the interim there have been substantial changes in transplant practice, from the introduction of high resolution molecular typing for volunteer unrelated donors, the introduction of RIC regimens and improvements in supportive care, all of which have potentially resulted in better transplant outcomes and thus making the results of earlier reports difficult to interpret.

Myeloablative HSCT

Conventional MA regimens, such as cyclophosphamide combined with total body irradiation (CYTBI) or busulfan (BUCY), may produce good OS rates. Patients treated with BUCY, with targeting of BU dose, had a 5-year OS of 68%, compared to 46% in non-targeted regimens (Deeg *et al*, 2003; Kerbauy *et al*, 2007; Zang & Deeg, 2009). Treatment-related mortality (TRM) at 1 year following MA HSCT ranged from 16% to 48%, with better outcomes seen in recipients of stem cells from human leucocyte antigen (HLA)-matched related donors (Guardiola *et al*, 1999; Daly *et al*, 2003; Ditschkowski *et al*, 2004; Kerbauy *et al*, 2007; Ballen *et al*, 2010; Stewart *et al*, 2010; Abelsson *et al*, 2011). OS $\geq$ 3 years varied from 30% to 61% while reported progression-free survival (PFS) of $\geq$3 years ranged from 15% to 39% (Table V). T cell depletion (TCD), reduction in recipient and donor T cells mediated by anti-T cell antibodies, may reduce PFS (Guardiola *et al*, 1999).

Reduced Intensity HSCT

Step-down development of MA regimens in the past two decades led to RIC regimens, in an effort to reduce early TRM, often using fludarabine (FLU) and including, in this guideline, non-myeloablative protocols, such as TBI 200 cGy. Some incorporate TCD manoeuvres, such as addition of anti-lymphocyte globulin(ALG). Following the initial success of RIC-HSCT in myelofibrosis (Devine *et al*, 2002; Rondelli *et al*, 2005), a variety of RIC regimens have been explored, for example, FLU TBI 200 cGy, FLU BU ALG, FLU melphalan alemtuzumab, FLU BU alemtuzumab and CY thiotepa. Larger retrospective studies with prolonged follow-up suggested TRM at day 100 and 1 year of 5·8–21% and 15–49%, with OS and PFS $\geq$ 3 years about 31–67% and 17–51%, respectively (Table V).

Patient selection for HSCT

Disease status. Advanced disease was associated with poorer survival post-HSCT (Kerbauy *et al*, 2007; Kröger *et al*, 2009a; Ciurea *et al*, 2010; Scott *et al*, 2010; Samuelson *et al*, 2011) while the *JAK2* V617F mutation (Kröger *et al*, 2009b) or antecedent PV/ET may result in superior survival (Kerbauy *et al*, 2007). Transfusion dependency characterizes aggressive disease, with worse HSCT outcome, although iron chelation may ameliorate (Bacigalupo *et al*, 2010; Leitch *et al*, 2010; Elena *et al*, 2011).

The European Leukaemia Network consensus is that allograft should be considered when non-HSCT prognosis is <5 years, currently considered as those with IPSS Intermediate 2 or High risk disease (Barbui *et al*, 2011). The modified IPSS prognostic scores, namely DIPSS and DIPSS-Plus, may give further refinement to patient selection (Scott *et al*, 2012).

Patient co-morbidity. Advancing age and HSCT co-morbidity index 4–6 confer poorer outcomes post-HSCT in myelofibrosis (Sorror *et al*, 2005; Kerbauy *et al*, 2007; Zang & Deeg, 2009; Abelsson *et al*, 2011). Nevertheless, consecutive patients aged 60–78 years have had day 100 TRM of 13% associated with a 3-year PFS of 40% (Samuelson *et al*, 2011). Massive splenomegaly >22 cm may predict TRM and relapse (Bacigalupo *et al*, 2010). Splenectomy pre-HSCT generally leads to earlier engraftment, without impact upon OS or graft failure (Guardiola *et al*, 1999; Daly *et al*, 2003; Kerbauy *et al*, 2007; Ballen *et al*, 2010) although relapse risk may be increased Kröger *et al* (2009a). Splenectomy is generally not recommended pre-HSCT.

Donor and graft characteristics. Most HSCT in myelofibrosis utilize adult HLA-matched family/volunteer donors, with superior outcomes in 10/10 HLA-matched donors (Kröger *et al*, 2009a) and higher cell doses (Guardiola *et al*, 1999). Umbilical cord stem cell HSCT has also been successful (Takagi *et al*, 2010). Use of HLA-mismatched donors increases the risk of graft failure (Ballen *et al*, 2010), necessitating stem cell reinfusion (Kröger *et al*, 2009a). Acute GvHD grade II–IV and extensive chronic GvHD were reported in 27% and 25% of cases respectively, in the TCD setting (Kröger *et al*, 2009a) compared to 64% and 59% in a predominantly non-TCD cohort (Kerbauy *et al*, 2007). However, the presence of chronic GvHD may improve OS (Kröger *et al*, 2009a). The optimal GvHD prophylaxis is unclear (Soiffer *et al*, 2011). Donor lymphocyte infusions may reverse clinical or *JAK2* V617F molecular relapse/persistence

post-HSCT (Byrne *et al*, 2000; Benjamini *et al*, 2008; Kröger *et al*, 2009b).

Recommendations for Allo-HSCT

Definition: A transplant–eligible patient is defined as one deemed fit enough to undergo the procedure with manageable co-morbidities and having an HLA-matched sibling or unrelated donor available.

- **Transplant-eligible patients <45 years of age, with an IPSS risk of Intermediate 2 or High, especially with transfusion dependence and/or adverse cytogenetic abnormalities, should be considered for MA allo-HSCT (Evidence level 2, Grade C).**
- **Transplant-eligible patients with an IPSS risk of Intermediate 2 or High, especially with transfusion dependence and/or adverse cytogenetic abnormalities, together with an HSCT co-morbidity index ≥ 3, or who are aged over 45 years, should be considered for RIC allo-HSCT (Evidence level 2, Grade C).**
- **Patients should be transplanted before they have received more than 20 units of red cells (Evidence level 2, Grade C).**
- **Use of oral busulfan should be accompanied by targeted dosing according to plasma levels. Alternatively, intravenous busulfan can be used, guided by plasma levels where possible (Evidence level 2, Grade C).**
- **There is no convincing evidence for pre-transplant splenectomy and some evidence of harm both from surgical morbidity and mortality and a possible increased risk of relapse post-transplant (Evidence level 2, Grade C).**
- ***JAK2* V617F mutated patients monitored by quantitative polymerase chain reaction (Q-PCR) post-transplant who do not achieve or who relapse from molecular CR are candidates for donor lymphocyte infusions in the absence of GvHD (Evidence level 2, Grade B). The role of Q-PCR for other mutations post-bone marrow transplantation remains unclear.**
- **There is no conclusive evidence to support use of a specific MA or RIC conditioning regimen, although favourable results have been achieved following BUCY and FLUBU and anti-lymphocyte globulin. Every effort should be made to enrol patients in prospective clinical studies and data should be reported to National and International Registries (Evidence level 2, Grade C).**

Blast phase of myelofibrosis

Diagnosis. The blast phase of myelofibrosis (either PMF, post-PV MF or post-ET MF) is synonymous with acute myeloid leukaemia (AML). According to the consensus on terminology determined by the IWG-MRT, such an event is termed blast phase PMF (PMF-BP; Mesa *et al*, 2007). PMF-BP has been defined by either (i) meeting the typical WHO 2009 criteria for AML in the setting of a known prior diagnosis of MF (Vardiman *et al*, 2009) or, (ii) a persistent increase in peripheral blood blasts to a level >20% for 8 weeks (Tefferi *et al*, 2006a). The latter criteria, based on circulating blasts, enables the diagnosis to be made in those individuals in whom an aspirate is not possible and for those whose trephines are almost completely replaced by fibrosis, making an estimation of blast percentage very difficult.

Prognosis. The literature concerning the prognosis is limited, but suggests that the majority of individuals with PMF-BP will survive <1 year, with many dying within 6 months, despite therapeutic options that have been historically available (Mesa *et al*, 2005). There is no evidence that the prognosis, or therapeutic response, differs in PMF-BP arising from PMF, post-ET, or post-PV MF.

Establishing the therapeutic goal. Despite the limitations of available data, it is clear that; (i) the prognosis with PMF-BP is poor, sometimes despite maximal efforts; (ii) AML induction regimens are active in PMF-BP, but response rates appear lower than those for *de novo* AML and (iii) responses to AML induction are likely, at best, to result in a short return to chronic phase disease.

Prolongation of survival as goal. There is no convincing evidence that medical therapies prolong survival in PMF-BP. However, following the encouraging results of azacitidine in high risk MDS, a recent study evaluated its efficacy in transformed MPN (Thepot *et al*, 2010). An overall response rate of 38% was reported, including 4/7 cases of transformed PMF with a resultant median survival of 8 months. Consideration, therefore, can be given to azacitidine, 75 mg/m^2 for 7 d every 28 d as a single agent, although further data is needed to confirm its efficacy in this setting.

Curative goal. A curative path for PMF-BP is difficult, but not impossible to achieve, based on the following observations. Firstly, allo-SCT is the only therapy likely to lead to long-term remission or cure of PMF-BP. Secondly, in line with the current management of other myeloid neoplasms, allo-SCT should be performed as soon as chronic phase has been re-established following intensive chemotherapy. Such a view is based on the experience in MDS and blast phase of chronic myeloid leukaemia, where transplantation in the presence of a significant tumour burden (i.e. blasts >20%) results in a very high risk of relapse. Indeed, a recent report from the M.D.Anderson Cancer Center suggests that this approach is feasible for a small proportion of patients with PMF-BP (Ciurea *et al*, 2010). There are few data, however, to support the use of a particular induction regime. Despite the interesting reports of individual cases returning to chronic phase following azacitidine therapy, its use as a bridge to SCT should be viewed as experimental.

Once a resumption of chronic phase MF is achieved, allo-SCT should be undertaken as soon as possible. Choice of the

conditioning regimen is unclear, although RIC is best reserved for those patients who have completely returned to a chronic phase disease.

Recommendations for PMF-BP

- **PMF-BP has a poor prognosis and consideration should be given to strictly supportive care (Evidence level 2, Grade B).**
- **Azacitidine (75 mg/m^2 for 7 d every 28 d) as a single agent can lead to responses of a palliative or, possibly, life-prolonging nature for patients who will not be candidates for allo-SCT (Evidence level 2, Grade C).**
- **A curative approach for PMF-BP requires the success of induction chemotherapy, with a return to a chronic phase disease, and an immediate allogeneic stem cell transplant. Rigorous candidate selection is needed, given that these challenging steps are likely to be successful in only a minority of patients (Evidence level 2, Grade B).**

Management of pregnancy

MPN-MF is rare in patients of childbearing age and the very few available case reports have been summarized in a paper describing the UK experience (Tulpule *et al*, 2008). This study suggested that adverse fetal and maternal events can occur in pregnancy, but to date there is no evidence for disease progression. Management guidance is hampered by lack of evidence, but the algorithm suggested in the BCSH guidelines for thrombocytosis is suggested (Harrison *et al*, 2010).

Recommendations

- Pregnancy is a rare event in PMF and data should be prospectively collected. Management according to current guidelines for ET is recommended (Evidence level 2, Grade C).

PMF in childhood

Great effort must be undertaken in making a definitive diagnosis of PMF in a child, since not only is the condition rare, but many cases with a typical phenotype may be polyclonal. Clearly, the detection of either a *JAK2* V617F or *MPL* W515L will confirm a diagnosis of MPN, although currently there are no genetic data available for children. Diagnostic difficulty can arise with the following disorders, especially if an adequate cytogenetic preparation is not obtained;

- acute panmyelosis with myelofibrosis
- acute megakaryoblastic leukaemia (AMKL, in Down syndrome)
- autoimmune disorders, Natural Killer cell proliferation
- familial cases of infantile myelofibrosis
- causes of secondary myelofibrosis, e.g. rickets
- hypocellular MDS

Many cases presenting in infancy may eventually 'burn out', with spontaneous erythropoietic recovery occurring as early as 2–3 years after diagnosis (Altura *et al*, 2000). Therefore, a conservative approach is recommended for such patients and a trial of steroids should be considered, once AMKL and rickets (Bhakhri & Debata, 2010) have been excluded. The only curative option for 'true' PMF is an allogeneic BMT. However, this option should not be undertaken lightly and should be restricted to patients for whom all other diagnoses have been excluded, particularly for those with intractable symptomatic cytopenias, or a rising blast count.

Recommendations for PMF in children

- **A conservative approach is recommended for most cases. A trial of steroids should be considered, once AMKL and vitamin D deficiency have been excluded (Evidence level 2, Grade B).**

Novel therapies

A number of potential therapies are under evaluation, either alone, or in combination for PMF. JAK inhibitors show the most exciting results in controlling two difficult aspects of PMF, namely splenic enlargement and debilitating symptoms. Indeed they represent the only therapeutic modality, with the exception of BMT, to deliver sustained and meaningful responses. The future, however, probably lies in combining these modalities.

JAK inhibitors

The results from clinical trials in patients with MPN-MF are currently available for a number of agents; one of which has data from Phase III studies (Verstovsek *et al*, 2012). Additional JAK inhibitors are currently in early phase trials with limited data. These agents appear to deliver unprecedented responses in quality of life and splenomegaly; this may also include a survival benefit in the case of INC424 (or ruxolotinib) and has been demonstrated in comparison to placebo or best available therapy (Harrison *et al*, 2012; Verstovsek *et al*, 2012).

Recommendations

- **A number of JAK inhibitors are at various stages of clinical development and a consistent pattern of response in splenomegaly and disease-related symptoms is emerging. Initial data from a Phase III study suggests survival may be improved. Further data with regards to effects upon survival and leukaemic transformation are awaited. Cur-**

rent recommendation to consider referring patients, who have failed hydroxycarbamide therapy and are not presently suitable for BMT, for trials with JAK inhibitors (Evidence level 1, Grade A). Should these agents be approved then they would be considered as first-line agents for patients with troublesome splenomegaly and disease-related symptoms (Evidence level 1, Grade A).

- **See additional recommendations with regard to splenomegaly and management of symptoms.**

Summary of recommendations

Molecular diagnostic investigations

- *JAK2* V617F mutation screening should be carried out routinely in patients with PMF. Quantitative results are not required for clinical management.
- *BCR-ABL1* rearrangement should be excluded in cases with atypical trephine biopsy features, or if the patient lacks a mutation in *JAK2* or *MPL*.
- *PDGFRA* and *PDGFB* rearrangements should be excluded in the presence of significant eosinophilia. (Screening for other mutations remains a research tool and routine screening cannot be justified, apart from in cases of diagnostic difficulty where detection of a clonal abnormality would be informative) (Evidence level 2, Grade B).

Therapeutic decisions

- Therapeutic decisions, especially regarding the use of allo-SCT, should be based on the patient prognosis as determined by the IPSS (at diagnosis), or the IPSS's recent modifications, i.e. the DIPSS or DIPSS Plus (during follow-up). Note that no prognostic score has been validated for either post-PV MF or post-ET MF.
- Whilst the IPSS, DIPSS and DIPSS Plus have not been validated for post-PV MF and post-ET MF, it is suggested that they still be used in this setting (Evidence level 2, Grade C).

Recommendations for the medical management of splenomegaly

First Line:

- Hydroxycarbamide (in the absence of cytopenias).
- Thalidomide and prednislone (in presence of cytopenias) – consider lenalidomide (if anaemic with platelet count $>100 \times 10^9$/l).

Second Line:

- Consideration should be given to the use of JAK inhibitors either as part of a clinical trial, or via patient access protocols until widely available. These agents are now approved in the USA for first-line therapy, which is appropriate following approval (Evidence level 1, Grade A).

Recommendations for splenectomy

Indications

- Drug-refractory symptomatic splenomegaly.
- Drug-refractory anaemia.
- Symptomatic portal hypertension (e.g. ascites, bleeding varices).
- Severe catabolic symptoms including cachexia (Evidence level 2, Grade C).

Peri-operative management

- Evaluate cardiac, hepatic, renal and metabolic status.
- Correction of any coagulopathy.
- Meticulous control of platelet count pre- and post-splenectomy.
- Laparoscopic splenectomy not advised.
- Splenic artery embolization not advised.
- Appropriate vaccination and long-term penicillin (Evidence level 2, Grade C).

Post-splenectomy myeloproliferation

- Cytoreductive therapy (hydroxycarbamide). Cladribine can be considered in selected patients (Evidence level 2, Grade C).

Recommendations for radiotherapy

- Patients with symptomatic splenomegaly, who have an adequate platelet count ($>50 \times 10^9$/l) and who are not deemed suitable for surgical intervention.
- EMH involving vital organs.
- Severe bone pain (Evidence level 2, Grade C).

Transfusion recommendations

- Red cell transfusions are recommended in PMF patients with symptomatic anaemia (Evidence level 2, Grade B).
- Iron chelation therapy is not routinely recommended in PMF (Evidence level 2, Grade B).

Recommendations for erythropoietin

- A trial of rEPO therapy should be considered in anaemic PMF patients with inappropriately low EPO levels (<125 u/l). Responses are more likely in those with relatively moderate anaemia (Evidence level 2, grade B).
- rEPO should be commenced at a dose of 10 000 units three times weekly (or darbepoietin 150 μg weekly,

doubling to 20 000 three times weekly (darbepoietin 300 μg weekly) after 1–2 months in the absence of an early response. Treatment should be discontinued after 3–4 months if no response occurs (Evidence level 2, grade B).

Recommendations for androgen therapy

- Danazol should be considered as a therapeutic option to improve the haemoglobin concentration of patients with myelofibrosis and transfusion-dependent anaemia (Evidence level 2, Grade B).
- Recommended starting dose is 200 mg daily, with a gradual dose escalation, depending on tolerability and patient weight (to a maximum of 600 mg daily for patients <80 kg and 800 mg for patients >80 kg) (Evidence level 2, Grade B).
- Patients should be treated for a minimum period of 6 months. Responding patients should be maintained for a further 6 months on 400 mg daily before titrating down the dose to the minimum required in order to maintain a response (Evidence level 2, Grade B).
- LFTs should be monitored at least monthly initially and liver ultrasound is recommended every 6–12 months to exclude hepatic malignancy (Evidence level 2, Grade C).
- Male patients should be screened for prostate cancer before and during therapy (Evidence level 2, Grade B).

Recommendations for management of consitutional symptoms

- Management of consitutional symptoms in PMF is challenging and there is no evidence of benefit for conventional agents in this area. Patients with profound symptoms are usually in the poor risk group and should be considered for experimental therapy wih JAK inhibition (Evidence level 1, Grade A).

Recommendations for myelosuppressive therapy

- Hydroxycarbamide is the first-line choice for the control of the hyperproliferation manifestations of myelofibrosis (Evidence level 2, Grade B).
- Anagrelide should be used with caution in patients with established myelofibrosis (Evidence level 2, Grade B).
- The use of IFN-α in PMF patients should be restricted to cases with early phase disease with more proliferative disease features (Evidence level 2, Grade B).
- High starting doses of conventional IFN-α are very poorly tolerated in PMF and should be avoided. When conventional IFN-α is used, it is recommended to commence at 1·5 million units three times per week and increase to a maximum of 15 million units/week as tolerated. If using pegylated-IFN, α2a is the recommended agent (Evidence level 2, Grade B).

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- Transplant-eligible patients with an IPSS risk of Intermediate 2 or High, especially with transfusion dependence and/or adverse cytogenetic abnormalities, together with an HSCT co-morbidity index ≥ 3, or who are over the age of 45, should be considered for RIC allo-SCT (Evidence level 2, Grade C).
- Patients should be transplanted before they have received more than 20 units of red cells (Evidence level 2, Grade C).
- Use of oral busulfan should be accompanied by targeted dosing according to plasma levels. Alternatively, intravenous busulfan should be used, guided by plasma levels where possible (Evidence level 2, Grade C).
- There is no convincing evidence for pre-transplant splenectomy and some evidence of harm both from surgical morbidity and mortality and a possible increased risk of relapse post-transplant (Evidence level 2, Grade C).
- *JAK2* V617F mutated patients monitored by Q-PCR post-transplant who do not achieve or who relapse from molecular CR are candidates for donor lymphocyte infusions in the absence of GvHD (Evidence level 2, Grade B). The role of Q-PCR for other mutations post-BMT remains unclear.
- There is no conclusive evidence to support use of a specific MA or RIC conditioning regimen, although favourable results have been achieved following BUCY and FLUBU and anti-lymphocyte globulin. Every effort should be made to enrol patients in prospective clinical studies and data reported to National and International Registries (Evidence level 2, Grade C).

Recommendations for management of PMF-BP

- The blast phase of PMF has a poor prognosis and consideration should be given to strictly supportive care (Evidence level 2, Grade B).
- Azacitidine (75 mg/m^2 for 7 d every 28 d) as a single agent can lead to responses of a palliative, or possibly life prolonging, nature for patients who will not be candidates for allo-SCT (Evidence level 2, Grade C).
- A curative approach for PMF-BP requires the success of induction chemotherapy, with a return to a chronic phase disease, and an immediate allogeneic stem cell transplant. Rigorous candidate selection is needed, given that these challenging steps are likely to be successful in only a minority of patients (Evidence level 2, Grade B).

Recommendations for management of pregnancy

- Pregnancy is a rare event in PMF and data should be prospectively collected. Management according to current guidelines for ET is suggested (Evidence level 1, Grade C).

Recommendations for management of PMF in children

- A conservative approach is recommended for most cases. A trial of steroids should be considered, once AMKL and vitamin D deficiency have been excluded (Evidence level 2, Grade B).

Recommendations for use of novel therapies (*JAK inhbitors*)

- A number of JAK inhibitors are at various stages of clinical development and a consistent pattern of response in splenomegaly and disease-related symptoms is emerging. Initial data from a Phase III study suggests survival may be improved. Further data with regards to effects upon survival and leukaemic transformation are awaited. Current recommendation to consider referring patients, who have failed hydroxycarbamide therapy and are not presently suitable for BMT, for trials with JAK inhibitors (Evidence level 1, Grade A). Should these agents be approved then they would be considered as first-line agents for patients with troublesome splenomegaly and disease-related symptoms (Evidence level 1, Grade A).
- See additional recommendations with regard to splenomegaly and management of symptoms.

Disclaimer

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