Use of JAK inhibitors in the management of myelofibrosis: a revision of the British Committee for Standards in Haematology Guidelines for Investigation and Management of Myelofibrosis 2012

The British Committee for Standards in Haematology (BCSH) Guidelines for myelofibrosis were produced in 2012 (Reilly *et al*, 2012), but since then Ruxolitinib, a JAK1/JAK2 inhibitor, has been approved for use in the European Union and highly prevalent mutations in the Calreticulin gene (*CALR*) have been described. We therefore wish to revise the existing guideline (Reilly *et al*, 2012) to accommodate this important data. Current diagnostic criteria should be modified to incorporate testing for the *CALR* mutations into major criteria A2 alongside *JAK2* V617F, as shown in Table I (*Evidence grade 1A*). Patients with *CALR* mutations may have a better prognosis (Klampfl *et al*, 2013), but this has not formally been assessed and incorporated into prognostic scores.

Substantial data are now available concerning responses to JAK inhibitor therapies including beneficial effects upon survival (Verstovsek *et al*, 2012, 2013; Cervantes *et al*, 2013). For example, at 144 weeks in the COMFORT-II study the median of overall survival had not been reached in either arm. A total of 29 (19·9%) and 22 (30·1%) patients died during the study in the ruxolitinib and best available therapy (BAT) arms, respectively, of which deaths on treatment were reported for 13 (8·9%) in the ruxolitinib arm, and 5 (6·8%) in the BAT arm (one death occurred after crossover to ruxolitinib). There was a 52% reduction in risk of death in the ruxolitinib treatment arm compared to the BAT arm (Hazard Ratio = 0·48, 95% confidence interval 0·28–0·85). The estimated probability of being alive at 144 weeks was 81% in ruxolitinib arm and 61% in BAT arm. The *P*-value for the log-rank test stratified by the baseline risk category was 0·009, (Cervantes *et al*, 2013). Furthermore, data from these randomized studies suggest that standard therapies are comparable to placebo in terms of spleen and symptom responses. The previous guideline (Reilly *et al*, 2012) recommended consideration of JAK inhibitor therapy for patients who have failed hydroxycarbamide therapy and are not presently suitable for bone marrow transplantation, or for patients with severe constitutional symptoms. In view of new evidence we now formally recommend ruxolitinib as first line therapy for symptomatic splenomegaly and/or myelofibrosis-related constitutional symptoms regardless of *JAK2* V617F mutation status (*evidence grade 1A*) where the balance between need to resolve the latter outweighs risk of side effects and, in particular, we make the following recommendations:

Table I. 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, CALR* 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.

Indications:

1 Symptomatic splenomegaly. (*evidence grade 1A*)
2 Myelofibrosis-related symptoms that are impinging upon quality of life. (*evidence grade 1B*)
3 Hepatomegaly and portal hypertension due to myelofibrosis are reduced by ruxolitinib (Verstovsek *et al*, 2010) and it can be considered for these indications. (*evidence grade 2B*)

Whilst treatment with ruxolitinib is suggested to confer a survival advantage treatment with this agent in asymptomatic patients and/or those who lack bothersome splenomegaly is not currently recommended.

Tolerance and side effects:

1 Anaemia and thrombocytopenia are to be anticipated with this agent, anaemia usually peaking by weeks 12–16 and improving thereafter. In patients with pre-existing anaemia and thrombocytopenia (NB, those patients with

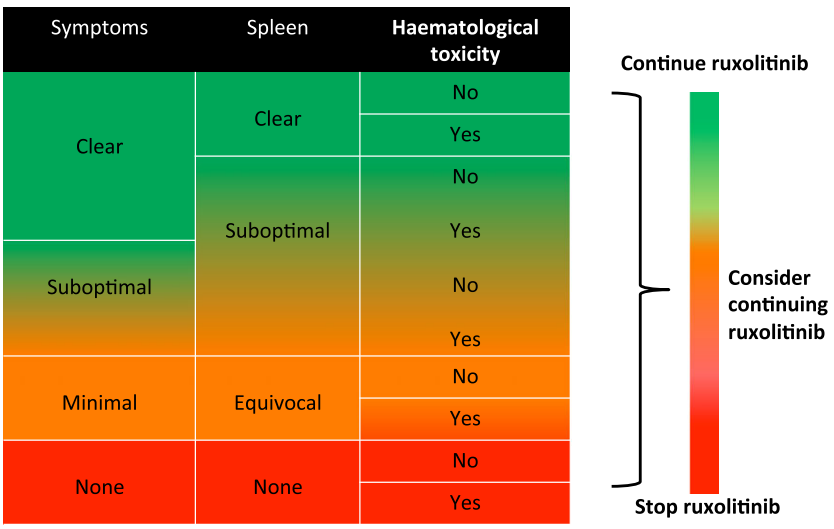

Fig 1. Treatment decisions with Ruxolitinib therapy: when to consider stopping. Clear benefit for symptoms and splenomegaly would take into account the treatment target. For example, in clinical trials the target spleen response was 50% reduction in palpable spleen length; this might differ in clinical practice. Suboptimal response would be improvement but not at target and equivocal or minimal might be stable or minimal reduction. Haematological toxicity would include anaemia, neutropenia and thrombocytopenia and also the occurrence of infections thought to be related to the drug.

platelet counts below 50 × 10^9/l are excluded from using this drug) a lower starting dose is recommended for example 5 mg BD (Harrison *et al*, 2013) (*evidence grade 1B*)

2 Anaemia may be ameliorated by lowering the dose of ruxolitinib or by concomitant use of erythropoietin-stimulating agents, and/or anabolic steroids, such as danazol (McMullin *et al*, 2011). (*evidence grade 2B*)

3 Given that there have been reports of reactivation of latent and atypical infections, such as hepatitis B and tuberculosis, the prescriber should actively screen for these and use appropriate prophylactic measures. Live vaccinations should be considered with caution. (*evidence grade 1B*)

Monitoring response:

1 For objective monitoring of symptoms, a tool such as the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)may be useful (Emanuel *et al*, 2012; Harrison *et al*, 2013). (*evidence grade 1A*)

2 Recent response criteria for testing novel myelofibrosis treatments have been suggested for use in clinical trials (Tefferi *et al*, 2013), although these are not intended or recommended for use in clinical practice.

3 The decision to stop ruxolitinib therapy will depend upon a combination of different factors, including benefit upon treatment target (usually spleen and/or symptoms) and presence or absence of toxicity. The degree of target spleen or symptom reduction has not yet been identified and will be individual for each patient. It is recommended that the dose should be modified to the maximum tolerated where response is not adequate and that treatment should be continued for 24 weeks. A schematic for considering whether to continue or stop these agents is suggested in Fig 1. (*evidence grade 1B*)

How to stop

1 Disease symptoms and splenomegaly will recur on drug withdrawal, sometimes rapidly. A gradual dose tapering over 7–10 d and avoidance of sudden interruptions are recommended. Cover with systemic steroids (suggestion 20–30 mg of prednisolone) has also been used in these circumstances (Harrison *et al*, 2013). (*evidence grade 1A*)

For patients failing or intolerant of ruxolitinib, additional JAK inhibitors are being assessed in clinical trials and may be approved in the future.

Authorship statement

The content was reviewed and approved by all authors, the manuscript was written by CH.

Competing interests

John T. Reilly has acted as consultant or been paid on the speakers bureau for Novartis and Shire. Mary Frances McMullin has acted as a consultant or been on the speakers bureau for Novartis, Sanofi, Shire and Gilead pharmaceuticals. Philip A. Beer, none. Nauman Butt has received sponsorship to attend educational meetings from Novartis and Shire Pharmaceuticals, and acted as a speaker for educational meeting sponsored by Novartis and Bristol-Myers Squibb. Eibhlin Conneally has acted as an advisory board member for Novartis, Bristol-Myers Squibb and Pfizer Pharmaceuticals. Andrew Duncombe has acted as an advisory board or speaker bureau member for Novartis, Sanofi, Amgen, Roche and Baxter. Anthony R. Green, none. N. George Mikhaeel, none. Marie H. Gilleece, none. Steven Knapper has acted as a consultant for Novartis and has received funding for overseas conference travel from Novartis, Shire. Adam Mead has received consultancy fees from Novartis and Sanofi Aventis and research

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