CASE REPORT

Treatment options for patients with primary myelofibrosis

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Abstract

Background  Primary myelofibrosis (PMF) is a myeloproliferative disorder resulting in progressive bone marrow fibrosis. In some PMF patients, a mutation in the gene coding for janus-associated kinase 2 (JAK2) results in cell proliferation and evasion of apoptosis. PMF typically occurs in older patients, and is associated with poor prognosis and low survival, with death occurring secondary to cardiovascular disease.(1) Investigations include full blood counts, blood film analysis, and bone marrow aspiration and trephine. Treatment is largely palliative; the single curative intervention of stem-cell transplant being available only to low-risk younger patients. Potential supportive treatments include the use of JAK2 inhibitors.

Method  This case report studies a patient who was diagnosed with PMF at the age of 60.

Results  The patient’s condition remained stable for up to 11 years before her symptoms deteriorated and her treatment was altered. The report focuses on current and upcoming treatments including JAK inhibitors, and evaluates their possible future implications for the management of patients with PMF.(2,3)

Conclusion  Breakthroughs in the understanding of the underlying PMF molecular mechanisms have led to improved treatments. There is a future role for JAK2 inhibitors in the management of palliative care. Ruxolitinib, which is now available for use in clinical practice, may alter treatment and improve quality of life for those living with PMF.
Introduction

The aims of this article are to gain an understanding of myelofibrosis (MF), including the pathophysiology, clinical presentation, investigations, and diagnostic and prognostic features. More specifically, it looks at current treatment options and future developments which could alter the disease course. In addition, through this case report, we aim to analyse the management of a patient with longstanding primary myelofibrosis (PMF) and to discuss currently available and emerging treatment options.

The current guidelines for the diagnosis and management of MF, published by the British Journal of Haematology in 2012, were used as the benchmark for current practice in this area. The management of the patient in our case report was compared to the standards laid out within these guidelines, and a subsequent review of the literature aimed to identify any advances in therapy since their publication.

Points raised in the discussion focus on the reasons for denial of specific treatments to the patient. It looks at future therapies and how they may be adapted for elderly patients (the majority of PMF patients) who currently are unsuitable for a number of treatment options. The only curative treatment is currently only suitable for younger patients, with strict controls on eligibility. A number of journals touch on advances in research into not only the understanding of the science behind myelofibrosis, but the combination of different therapies to achieve desired therapeutic goals.

Case presentation

In June 1998 a 60-year-old Caucasian woman was referred to the haematology department with thrombocytopenia and a suspected possible MF. At presentation to the haematology clinic, the patient had been bruising easily for the last four months; there was no history of bone pain, abdominal pain, night sweats or bleeding. The patient’s past medical history included hypothyroidism and asthma. She was a non-smoker and drank two units of alcohol a week. Her medication at the time included clomipramine, thyroxine, hormone replacement therapy and beclomethasone.

On examination the patient had petechiae over her shins, two small bruises on her sternum and right arm, and some generalised itching. There was no palpable lymphadenopathy, cardiovascular and respiratory systems were unremarkable, and abdominal examination revealed a marked splenomegaly, with the tip extending 3 cm below the umbilicus, and slight hepatomegaly.

A full blood count showed haemoglobin (Hb) 110 g/L, white blood cell count (WBCC) $4.1 \times 10^9/L$ and platelets $57 \times 10^9/L$. A peripheral blood film demonstrated increased reticulin with fine collagenisation; features consistent with an underlying MF. A bone marrow biopsy resulted in a dry tap and a
Trephine analysis showed marrow spaces which contained a marked increase in reticulin with fine collagenisation, in keeping with PMF. The majority of cells examined showed a translocation between the short arms of chromosomes 2 and 6 and an extra copy of chromosome 8, which is commonly found in myeloid disorders. Megakaryocytes were recognised with a few white cell precursors, although no definite evidence of malignancy was present.

The patient was initially treated with folic acid and iron tablets to maintain normal erythropoiesis.

The patient had good prognostic factors for her MF, there was no overt bleeding, and over the following years she has remained relatively well; however, her Hb and platelets remained low and her splenomegaly progressed. By 2009 the patient had been haematologically stable for 11 years with no constitutional symptoms; she was discussed in a multidisciplinary team (MDT) meeting where a decision for active monitoring was made. In 2010, owing to worsening anaemia, the patient underwent extensive investigation, and a JAK2 V617F mutation was detected. The patient had received some blood transfusions and was taking tranexamic acid and prednisolone owing to platelet deficiency, which level had dropped to 20–40 × 10^9/L. A CT scan revealed a small pericardial effusion, some lung consolidation, and diffuse sclerosis of the bones with multiple well-defined lytic areas; the patient's renal function was also declining (creatinine = 145 μmol/L, urea = 17 mmol/L, by 2011 estimated glomerular filtration rate = 36 ml/min/1.73 m²). An endoscopy showed a hiatus hernia, multiple ulcers and telangiectasia, and she was started on lansoprazole. In 2011 the patient was started on furosemide, ramipril, candesartan and spironolactone for symptoms of early heart failure. A further CT scan was performed owing to the deteriorating renal function that revealed three lesions in the spleen; these were discussed at a radiological MDT. The decision was taken not to biopsy the lesions because of the significant risk of bleeding. In October 2011 a chromosome analysis showed evidence of clonal evolution, with an unbalanced translocation between the long arms of chromosomes 1 and 11 resulting in trisomy 1q; this is a common finding in myeloproliferative neoplasia and is associated with disease transformation. The patient was referred for a trial involving a new JAK2 inhibitor in 2012, but was unfortunately ineligible owing to her decreased platelet count and thrombocytopenia being one of the possible side effects of the treatment. In 2013 the patient had been given immunoglobulin, Octagam and hydrocortisone for her MF, and is continuing with blood transfusions.

**Myelofibrosis**

MF is a myeloproliferative disorder; this term refers to disorders which involve clonal increase of the blood-forming cells in the bone marrow. Other myeloproliferative disorders include polycythaemia rubra
vera (PRV) and essential thrombocytopenia (ET). These disorders can be transitional and can evolve into one another over time. In PMF, fibrosis of the bone marrow occurs progressively and is secondary to hyperplasia of abnormal megakaryocytes. Fibroblasts are thought to be stimulated by cytokines and growth factors secreted by platelets and megakaryocytes. Anaemia may occur, resulting in extramedullary haemopoiesis in the spleen and liver, causing splenomegaly. Some patients may develop osteosclerosis. MF usually ensues after 50 years of age but sometimes presents in children; it may later transform to acute leukaemia.

Clinical features

Patients with MF can suffer from thrombocytosis or thrombocytopenia, leukocytosis or leukopenia, and ongoing anaemia. There are manifestations of constitutional symptoms such as low-grade temperature, night sweats and cachexia. Hepatomegaly due to extramedullary haemopoiesis results in symptoms such as pain, abdominal distension, early satiety, diarrhoea, dyspnoea, portal hypertension and splenic infarction.

Janus-associated kinase 2

A mutation (Val617Phe) in JAK2 (a tyrosine kinase in the cytoplasm of the bone marrow and blood) is present in nearly every patient with PRV, and half the patients with ET and MF. JAK2 transduces signals from various cytokines and growth factors that are involved in myeloid growth. Many haemopoietic growth factor receptors interact with a protein kinase. The cytoplasmic domains of the receptors move closer with growth factor binding. Concurrently the two JAK2 kinases are phosphorylated by each other and become activated. When mutation occurs it affects an area of the pseudo-kinase domain which negatively controls JAK2. The V617F mutation results in activation of the JAK molecules without the presence of a growth factor.

As JAK2 is activated, this results in cell survival and proliferation via three different paths. These include the phosphoinositide 3-kinase (PI3K) path with Akt (also known as protein kinase B), the signal transducer and activator of transcription (STAT) factors, and the activation of Ras leading to activation of mitogen-activated protein kinases (MAPK) and extracellular-signal-regulated kinases (ERK). The outcome is a collection of proteins that result in cell proliferation and survival.

Investigations and diagnosis

Blood films usually demonstrate the presence of myelocytes and normoblasts denoting a leukoerythroblastic reaction appearing as teardrop
poikilocytes. Because of fibrosis, a bone marrow aspiration typically results in a dry tap; trephine biopsies reveal atypical megakaryocytes which proliferate and show cytoplasmic and nuclear abnormalities – these are seen with collagen fibrosis and/or reticulin.\(^{(3,7)}\) Investigations should include screening for JAK2 V617F mutations. If patients lack this, a BCR-ABL1 genetic abnormality rearrangement should be sought if trephine biopsy shows uncharacteristic features and is representative of chronic myeloid leukaemia.\(^{(3)}\) Diagnosis is based on a mixture of clinical and histopathology findings, using the World Health Organization’s 2008 principles.\(^{(5,8)}\) Proven PMF is based on meeting all three major criteria and also two minor criteria from the WHO’s primary myelofibrosis diagnostic principles.\(^{(6)}\) The combination of the major and minor criteria helps rule out other disorders such as ET.\(^{(5)}\)

**Treatment**

Elderly patients with PMF tend to be treated conservatively. If they have no symptoms or low risk factors for further development of the disease, careful observation is adequate.\(^{(6)}\)

The most widely used agent for haemopoiesis and splenomegaly is hydroxycarbamide. Approximately 45% of patients respond within 8–10 weeks; cytopenias can develop at certain doses. Other drugs such as low-dose melphalan, interferon-alpha (IFN-\(\alpha\)), cladribine, and immunomodulatory drugs such as low-dose thalidomide when used in combination with prednisolone have produced weaker responses, often with myelosuppressive side effects. For treatment of splenomegaly, initially hydroxycarbamide should be used. If the patient suffers from cytopenias, then thalidomide and prednisolone should be used simultaneously. Medical therapies are the preferred treatment for splenomegaly; however, the use of splenectomy is also well established. It should only be carried out in patients with specific factors such as hypercatabolic symptoms, splenic infarction, refractory haemolysis, portal hypertension and symptomatic splenomegaly, and not before the patient has been assessed for hepatic, renal, cardiac, metabolic and haemostatic risks. Other risks include hepatic enlargement due to extramedullary haemopoiesis, and thrombocytosis leading to an elevated thrombotic risk; hence the requirement for normalisation of platelet counts pre- and post-splenectomy. Cytoreductive therapy post-surgery includes hydroxycarbamide and cladribine as a palliative option. Patients who are inappropriate for surgery with symptoms of splenomegaly and a platelet count of more than 50 \(\times\) 10\(^9\)/L may gain some relief and a relative decrease in their spleen size. Reduction in size is temporary and severe cytopenia can be a side effect requiring platelet transfusion. Therefore, radiotherapy is not an alternative for patients who are eligible for surgery.\(^{(4)}\)
Blood transfusions are recommended for the treatment of anaemia in PMF. This is the standard therapy; however, patients must be assessed individually. Chronic use of blood transfusions may lead to the patient developing iron overload; fortunately, this does not affect patient survival and there is no indication to use chelation therapy. Erythropoietin (EPO) is limited to PMF patients with low endogenous EPO levels (below 125 μ/l). Androgens have various results in anaemic patients. Danazol is the first line androgen therapy for PMF patients receiving blood transfusions for anaemia; it has additional roles in recovering platelet numbers and spleen size reduction. Side effects include hepatic tumours, deranged liver function tests (LFTs), increased libido, fluid retention and hirsutism. Thus it is recommended that LFTs are reviewed regularly and liver ultrasound scans (USS) are carried out every 6–12 months to exclude hepatic disease for patients receiving danazol. Prostate cancer screening should also be carried out on male patients.⁴

Fatigue, weakness, night sweats, bone pain, abdominal pain, weight loss, pruritus and cachexia represent the main constitutional symptoms of PMF. Increased pro-inflammatory cytokines and splenomegaly cause these incapacitating symptoms in advanced stages of the disease and according to Scherber et al., as cited by Reilly et al.⁴ – quality of life for PMF patients is similar to that of patients suffering from metastatic cancer. There is no evidence of benefit from conventional agents for the treatment of constitutional symptoms in PMF. Randomised clinical trials (Harrison et al. in 2012, Verstovsek et al. in 2012) have demonstrated possible benefit of JAK inhibitors on these symptoms.⁴

In order to control thrombocytosis; leukocytosis; and symptoms such as bone pains, night sweats, fatigue and weight loss which are associated with hypercatabolism and splenomegaly, myelosuppressive therapy is indicated. First-line medication for hyperproliferation includes hydroxycarbamide. Anagrelide, although linked with an increase in reticulin which is an important prognostic parameter associated with a worse life expectancy, can be used with caution with appropriate reviews of MF in patients. In early stages of the disease IFN-α should only be used in patients with proliferative features as it has been shown to slow the disease and even show regression of the fibrosis.⁴,⁹

Allogeneic haemopoietic stem cell transplantation (allo-HSCT) has a potentially curative effect with regression in bone marrow fibrosis. However, the reports have been non-comparative. The toxicity associated with the standard doses limits its availability to young patients, excluding the bulk of patients with PMF. Reduced intensity conditioning (RIC) is now widely available to elderly patients, in whom it broadens the applicability of allo-HSCT; it is based on eradicating neoplastic cells through the graft-vs-tumour effect.⁴,⁶ Patients are only able to undergo bone marrow transplantation if they have manageable co-morbidities, have a human
leukocyte antigen (HLA)-matched donor, and are well enough for the procedure. Patients who should be considered for myeloablative (MA) allo-HSCT include those under the age of 45 with an international prognostic scoring system (IPSS) of intermediate 2 or higher, and who are having blood transfusions and/or have adverse cytogenetic irregularities. Similar patients over the age of 45 should be considered for RIC allo-HSCT. Bone marrow transplantation should take place before the patient has had 20 units of blood transfusions. Plasma levels are used to estimate dosing of oral busulfan; IV busulfan can be given provided dosage is estimated using plasma levels. Increased risk of relapse may be seen in patients who have undergone splenectomies prior to transplant.\(^{(4)}\)

**JAK2 inhibitors**

Present management options for PMF, which include androgens, thalidomide, transfusions and myelosuppressive medications, do not alter the course of the disease. Discovery of JAK2 mutations in approximately half of PMF patients has led to new research.\(^{(10)}\) JAK inhibitors are one of a few potential treatments that are being currently examined. They are concerned with improving the symptoms of PMF and spleen enlargement and have shown consistent responses. Patients who are not eligible for bone marrow transplants and have not benefited from hydroxyurea-mide treatment should be recommended for JAK inhibitor randomised controlled trials.\(^{(4)}\) Currently they are not available for clinical use, but JAK inhibitors may be suitable as first-line treatment for patients with constitutional symptoms and splenomegaly.\(^{(4,10)}\) The JAK2 trials which have been described show active control of constitutional symptoms and splenomegaly in patients resistant to hydroxyurea and alternative management options. Unfortunately they were less successful in improving anaemia. JAK2 inhibitors including CYT387, AZD1480, SB1518 and LY2784544 were not able to encourage any remission of PMF or eliminate the mutated JAK2 clone. Responses were not dependent on the JAK2 mutational status, meaning that it was not clear whether their benefits were due to inhibition of JAK2 in neoplastic cells or from a global down-regulation of the proinflammatory cytokine signalling.\(^{(6)}\)

Ruxolitinib is a powerful JAK1 and JAK2 inhibitor that is approved for the management of high-risk and intermediate myelofibrosis.\(^{(11)}\) It selectively inhibits JAK2 V617F-driven Ba/F3 cell proliferation. This results in reduced activation of STAT factors by reduced phosphorylation of JAK2. In 2012, Harrison et al.\(^{(12)}\) evaluated the efficacy of ruxolitinib when compared with the ‘best available therapy’, which included commercially available monotherapies or combination therapies such as antineoplastic agents (hydroxyurea) and glucocorticoids. Using MRI or CT they found that 28% of the patients on ruxolitinib had a 35% spleen volume reduction,
compared with 0% in patients on the ‘best available therapy’. By just under a year, the mean palpable spleen length had decreased by 56% in the ruxolitinib patients but with the ‘best available therapy’ it had increased by 4%. Patients taking ruxolitinib also had improved symptoms and quality-of-life scores. However, side effects included thrombocytopenia and anaemia; these were treated by postponing treatment, dose reduction or blood transfusion. Studies so far have shown that continuous therapy with ruxolitinib can improve quality of life, reduce splenomegaly and PMF symptoms, and improve overall survival; however it does not reduce the rate of transformation to leukaemia and is not curative.\(^{(5,11,12)}\)

**Future treatments**

Other than allo-HSCT, management is palliative.\(^{(12)}\) However there are possible future treatments being investigated to improve the quality of management for patients with PMF. Improved efficacy against JAK2 V617F can be achieved by either reducing the JAK2 V617F allelic burden, or by inactivating the components of the signal transduction paths. Four types of treatment are being investigated; these include PIM kinase inhibitors, MEK inhibitors, histone deacetylase inhibitors (HDACis)/heat-shock protein 90 (Hsp90) inhibitors and PI3K/mTOR inhibitors.\(^{(5)}\)

PMF patients have increased histone deacetylase (HDAC) expression. The acetylation status of histones and other proteins is modulated by HDACis; this has effects such as cell-cycle and growth arrest, and inhibition of angiogenesis, cellular differentiation, apoptosis and immune surveillance. Consistent use of panobinostat, a pan-HDACi, has been shown in some cases to eliminate leukoerythroblastic blood features, resolve splenomegaly, improve anaemia, reduce symptoms, and feature regression of bone marrow fibrosis. Future studies will evaluate panobinostat and ruxolitinib used simultaneously to treat MF patients.\(^{(5)}\)

STAT and JAK2 are client proteins (also referred to as substrate proteins) for Hsp90, an ATP-dependent, dimeric molecular chaperone. Hsp90 stabilises these and folds them into their active configuration. Hsp90 inhibitors bind to the N-terminal ATP-binding domain of Hsp90 and inhibit this, resulting in proteasome-mediated degradation of the client protein in myeloproliferative neoplasm (MPN) cells.\(^{(6)}\)

PI3K/mTOR is involved in signalling for the cell proliferation and growth pathway involved in malignancies, including MF. DEZ235 is a dual PI3K/mTOR inhibitor that can cause MPN cells to undergo apoptosis.\(^{(5)}\)

**Prognosis**

Treatment of PMF such as allogeneic stem-cell transplantation (allo-SCT) depends on the patient’s prognosis. The IPSS is based on age, leukocyte
count, circulating blasts, Hb concentration and constitutional symptoms; it is used to classify patients with PMF into different risk groups. It has been modified recently to the dynamic IPSS (DIPSS) so that it can be used at any time during the course of the disease, and also the DIPSS plus, with the additional parameters of transfusion dependence, platelet count and unfavourable karyotype. It is recommended that the DIPSS plus be used when contemplating the use of allo-SCT.(4)

PMF has the worst prognosis of the MPNs; patients are classified into different risk groups which determine their survival. The median survival from diagnosis is approximately six years, with mortality occurring secondary to cardiovascular disease.\(^{(1,6)}\)

When PMF transforms to leukaemia, most patients survive for less than a year, with many dying within six months. Curative allo-SCT is the only treatment that could lead to the long-term remission of chronic leukaemia, but it is difficult to achieve.\(^{(4)}\)

**Discussion**

The patient studied is significant for a number of reasons. She had been managed conservatively for a number of years without the need for PMF medication. Her anaemia was controlled on folic acid and iron tablets for 12 years before any further deterioration, perhaps because she was diagnosed before such guidelines were recommended. In 2010 she was given blood transfusions when her anaemia became significant. She suffered from chronic thrombocytopenia and was eventually started on tranexamic acid and prednisolone.

Later in the disease the patient’s symptoms included massive splenomegaly but she did not receive any treatment such as hydroxycarbamide; this was probably owing to her significant thrombocytopenia. Additionally, the patient’s advanced age meant that she would not have been eligible for allo-SCT therapy. This is unfortunate as it is still the only management available with the potential to cure as long as there is no significant risk of mortality or morbidity. In the future as treatments are refined and dosage reduced, new transplant methods will simultaneously use JAK2 inhibition; this will allow PMF patients of increased age to become eligible for this type of management.\(^{(5)}\)

In 2012 the patient was referred for a ruxolitinib trial. The patient was regrettably denied, as two of the major side effects were anaemia and thrombocytopenia. This was unfortunate, as some of the recent reports concerning ruxolitinib have stated that they were able to manage the issues of anaemia and thrombocytopenia by briefly interrupting the therapy, reducing the doses, or simply discontinuing the treatment. Patients treated with ruxolitinib were able to continue with blood transfusions if needed.\(^{(12)}\)

Recent studies have led to the development of newer, highly specific JAK inhibitors, which reduce undesirable effects such as cytopenia.\(^{(13)}\)
The use of azacitidine in transformed MPN has shown promising results. In over half the cases reported there was a response resulting in a median survival of eight months. This may be a possible treatment for patients who have transformed PMF.\(^4\)

**Conclusion**

- In recent years, breakthroughs in the discovery of PMF molecular mechanisms and pathogenesis have led to improved treatments and the ongoing development of effective managements for the whole spectrum of PMF patients.\(^5\)
- There is likely to be a role for JAK2 inhibitors in the management of palliative care in patients with PMF regarding constitutional symptoms and splenomegaly.\(^6\)
- PMF is a difficult myeloid malignancy to manage effectively; elderly patients and co-morbid conditions limit the treatment options. Ruxolitinib is now available for use in clinical practice; its future applications may alter this treatment pattern and greatly improve the quality of life for those living with PMF.\(^5\)

**References**


