Myeloproliferative neoplasms: diagnosis, treatment and management of side effects

A Guide for Nurses

Leukaemia Care
Nurse Academy

Introduction

Myeloproliferative neoplasms (MPNs) are chronic blood cancers that arise due to a defect of the myeloid stem cells in the bone marrow which causes the production of too many abnormal blood cells that do not function properly.

Normal blood stem cells in the bone marrow develop in time into mature blood cells that include:

- Red blood cells: perform tissue oxygenation
- White blood cells: protect against infection and disease
- Platelets: facilitate clotting of blood

Production of new blood cells is normally very closely controlled so that it is balanced with the loss of worn-out cells or cells lost by bleeding or damage.

MPNs include three main disorders characterised by different excesses of blood cells in the blood and bone marrow:

- Polycythaemia vera (PV): Excess of red blood cells, but occasionally platelets and white blood cells
- Essential thrombocythaemia (ET): Excess of platelets.
- Myelofibrosis (MF): Excess of scar tissue (fibrosis) formed in the bone marrow that prevents the production of normal blood cells. MF can occur on its own (primary MF), or following PV or ET (secondary MF).

If you would like any information on the sources used for this booklet, please email **communications@leukaemiacare.org.uk** for a list of references.

In this booklet

About Leukaemia Care

Leukaemia Care is a national charity dedicated to ensuring that people affected by blood cancer have access to the right information, advice and support.

Our services

Helpline

Our helpline is available 9:00am – 5:00pm Monday - Friday and 7:00pm – 10:00pm on Thursdays and Fridays. If you need someone to talk to, call **08088 010 444**.

Alternatively, you can send a message via WhatsApp on **07500068065** on weekdays 9:00am – 5:00pm.

Nurse service

We have two trained nurses on hand to answer your questions and offer advice and support, whether it be through emailing **nurse@leukaemiacare.org.uk** or over the phone on **08088 010 444**.

Patient Information Booklets

We have a number of patient information booklets like this available to anyone who has been affected by a blood cancer. A full list of titles – both disease specific and general information titles – can be found on our website at **www.leukaemiacare.org.uk/support-and-information/help-and-resources/information-booklets/**

Support Groups

Our nationwide support groups are a chance to meet and talk to other people who are going through a similar experience. For more information about a support group local to your area, go to **www.leukaemiacare.org.uk/support-and-information/support-for-you/find-a-support-group/**

Buddy Support

We offer one-to-one phone support with volunteers who have had blood cancer themselves or been affected by it in some

way. You can speak to someone who knows what you are going through. For more information on how to get a buddy call **08088 010 444** or email **support@leukaemiacare.org.uk**

Online Forum

Our online forum, **www.healthunlocked.com/leukaemia-care**, is a place for people to ask questions anonymously or to join in the discussion with other people in a similar situation.

Patient and carer conferences

Our webinars provide an opportunity to ask questions and listen to patient speakers and medical professionals who can provide valuable information and support. For information on upcoming webinars, go to **www.leukaemiacare.org.uk/support-and-information/support-for-you/onlinewebinars/**

Website

You can access up-to-date information on our website, **www.leukaemiacare.org.uk**.

Campaigning and Advocacy

Leukaemia Care is involved in campaigning for patient well-being, NHS funding and drug and treatment availability. If you would like an update on any of the work we are currently doing or want to know how to get involved, email **advocacy@leukaemiacare.org.uk**

Patient magazine

Our magazine includes inspirational patient and carer stories as well as informative articles by medical professionals: **www.leukaemiacare.org.uk/communication-preferences/**

Clinical features and diagnostic characteristics of MPNs

Polycythaemia vera

Epidemiology and cause

- Rare disease with an incidence of 2-3 per 100,000 people per year.
- Most common in those aged over 60 years, however 20% occurs in those less than 40 years of age. More common in men than women.
- An excess of red blood cells makes the blood thicker than normal, predisposing patients to thrombosis, which is when blood clots block the flow of blood through the arteries and veins, potentially leading to heart attacks or strokes.

Thrombosis occurs in 30-50% of patients with PV Risk factors that increase the likelihood of blood clots or bleeding include:

- Being older than 60 years
- Having had previous blood clots or bleeding
- A high platelet count
- Having a cardiovascular risk factor, such as high blood pressure, diabetes, smoking or high cholesterol

The spleen becomes enlarged in up to 75% of patients as it makes red blood cells to compensate for the bone marrow not functioning correctly. More rarely, the liver may also be affected and become enlarged.

Exact cause of PV is unknown, however about 95% of patients with PV have a mutation, known as JAK2 V617F, in the protein Janus Kinase 2 (JAK2) that regulates blood cell production With current treatments, median survival for all patients with PV is 14 years, and 24 years in younger patients. Lifetime risk of transformation of PV to MF after 15 years is 6-14% and transformation to AML is 10-15%.

Symptoms and signs

Around 50% of patients with PV do not have any symptoms at diagnosis, and are identified during a routine full blood test

Common symptoms include:

- Fatigue

- Fever and night sweats
- Headaches with visual disturbances
- Dizziness or light headedness
- Weight loss
- Itching
- Enlarged spleen
- Reddish or purple skin
- Bleeding or clotting
- Bone pain and gout

Common complications which are responsible for the symptoms listed previously include blood clots in the arteries, which may lead to heart attacks, strokes and damage to the gastro-intestinal tract, and blood clots in the veins leading to venous thrombosis or pulmonary embolism.

Risk factors that increase the likelihood of blood clots or bleeding include:

- Being older than 60 years
- Having had previous blood clots or bleeding
- A high platelet count
- Having a cardiovascular risk factor, such as high blood pressure, diabetes, smoking or high cholesterol

Diagnosis

A diagnosis of PV requires the following criteria to be met

Haematocrit (volume of red blood cells expressed as a percentage of the total volume of blood cells) of:

- 52% or more for men (normal range: 41%-51%)
- 48% or more for women (normal range: 37%-47%)
- Presence of a JAK2 mutation, mainly the JAK2 V617F mutation
- For patients with no JAK2 mutation, the following criteria must be met
- Haematocrit (raised red blood cell mass) of 60% or more in men and 56% or more in women
- No secondary cause of the increase in red blood cells, such as disorders that cause oxygen deprivation of tissues or abnormal increase of, or sensitivity to, erythropoietin, a hormone which stimulates the bone marrow to produce red blood cells.
- Microscopic structure of the bone marrow consistent with PV

In addition, one of the following criteria must also be present to confirm a diagnosis of PV:

- Enlarged spleen which can be felt on examination or seen on X-ray or ultrasound
- Acquired gene mutation, other than BCR-ABL1, in the bone marrow cells

Clinical features and diagnostic characteristics of MPNs (cont.)

- Platelet count > 450x10^9/L (normal range: 150 and 450x10^9/L)
- Neutrophil white blood cell count >10x10^9/L in non-smokers or >12.5x10^9/L or more in smokers (normal range: 4.3-10x10^9/L). Neutrophils are white blood cells which protect the body against bacterial infections and inflammation
- Low serum erythropoietin

Essential thrombocythemia

Epidemiology and cause

Rare disease occurring in 1.5 to 3.0 per 100,000 people per year.

Most common in people aged over 60 years, but with a peak in younger women compared with men.

Most cases of ET are not inherited, except for 5-10% of patients who have familial ET. The clinical symptoms and mutations in familial ET resemble those in non-familial ET and PV (Jones and Cross 2013).

An excess of abnormal platelets make formation of blood clots more likely and these can obstruct the blood flow in the arteries and veins, potentially leading to heart attacks or strokes. White blood cell levels may also be elevated making the blood even thicker.

Thrombosis occurs in about 1% to 3% of patients per year, however in patients who have a JAK2 mutation, the incidence increases to 7.7% of patients per year. This results in:

- Heart attacks, strokes or damage to the gastro-intestinal tract due to blood clots in the arteries
- Venous thrombosis such as deep vein thrombosis in the calf
- Pulmonary embolism

The overall rate of haemorrhage in patients with MPN is less well defined with estimates ranging from 0.79% to 30% per patient per year. The risks of bleeding are increased if the platelet count is above 1000 to 1500x10^9/L (normal range: 150-450x10^9/L.

Patients with ET have near normal life expectancy. There is a very slight increased risk of transformation to MF of approximately 1% or AML of less than 1%.

Exact cause of ET is unknown; however ET patients have one of the following mutations:

- JAK2 in about 50-60% of patients
- Calreticulin (CALR) in 20-25% of patients
- Myeloproliferative Leukaemia virus gene MPL515L/K (MPL) in 2-3% of patients
- Patients with none of the three mutations above are known as triple negative patients and have a relatively good prognosis

Symptoms and signs

Patients with ET often have no symptoms at diagnosis and are identified during a routine full blood test.

Common symptoms of ET include:

- Fatigue
- Fever and night sweats
- Headaches
- Dizziness or light headedness
- Weight loss
- Spleen enlargement, present in 10-20% of ET patients at diagnosis and more commonly seen in young men
- Itching
- Reddish or purple skin
- Bone and joint pain

Risk factors that increase the likelihood of blood clots or bleeding include:

- Being older than 60 years
- Having had previous blood clots or bleeding
- A high platelet count
- Having JAK2 or MPL mutations
- Having a cardiovascular risk factor, such as high blood pressure, diabetes, smoking or high cholesterol

Diagnosis

Clinical features and diagnostic characteristics of MPNs (cont.)

A diagnosis of ET requires the following criteria to be present:

- Platelets ≥450x10^9/L
- Bone marrow biopsy showing an increase in the numbers of enlarged, mature megakaryocytes, which are the cells in the bone marrow that produce the platelets.
- Not meeting the World Health Organisation (WHO) diagnosis for other myeloid neoplasms such as PV or MF
- The presence of a JAK2, CALR or MPL mutation

If none of the above mutations are present, other causes of primary or secondary thrombocytosis and bone marrow examination typical of PV and MF must be excluded

Myelofibrosis

Epidemiology and cause

Rare disease with an incidence of 0.1 to 1 person per 100,000 persons per year.

Incidence is higher in men (0.59) than women (0.3).

Incidence by race is very similar, except for a noticeably higher incidence in those of Ashkenazi Jewish descent, where a family history is involved.

Median age at diagnosis is 64 years and it is very rare in children and young adults.

In the bone marrow, abnormal clonal blood stem cells (cell descended from, and genetically identical to, a single common ancestor) produce mature cells that reproduce abnormally quickly and cause scar tissue formation (fibrosis) in the bone marrow.

The bone marrow normally contains blood stem cells, that in time develop into mature blood cells. However, in patients with MF, abnormal stem cells take over the bone marrow, leading to chronic inflammation and fibrosis. This results in the bone marrow being unable to make enough normal blood cells to

carry out their functions.

To compensate for the abnormal production of blood cells, the spleen starts to produce blood cells causing it to enlarge. This is called extramedullary haematopoiesis and can also affect the liver and other sites to lesser degree.

Two main types of MF occur:

1. Primary MF that occurs spontaneously
2. Secondary MF in patients previously diagnosed with PV or ET

Primary or secondary MF are very similar in terms of symptoms and treatment.

Exact cause of MF is not known, however approximately 90% of patients with MF carry mutations in any of the following 3 genes.

80% of patients have one of three main gene mutations. These are:

- JAK2-V617F in approximately 60% of patients
- CALR in approximately 20% of patients
- MPL in approximately 10% of patients
- About 5-10% of patients do not have any of the gene mutations above and are known as 'triple-negative' MF patients (Tefferi et al 2014). Contrary to triple-negative ET patients, patients who have triple-negative MF have a poor prognosis.

Next generation gene sequencing, which looks at the presence of mutations in other relevant genes that may be implicated in the initiation and progression of MPNs is ongoing. This research may confirm that MPNs are caused by a combination of mutations in most patients.

Symptoms and signs

MF symptoms vary greatly between patients. Most patients have some symptoms when diagnosed , however others experience few or no symptoms at all in the early stages of MF.

Clinical features and diagnostic characteristics of MPNs (cont.)

Patients with MF may have any of the following symptoms or signs:

- Fatigue
- Sweating, predominantly at night
- Fever
- Enlargement of the spleen which can cause abdominal pain, discomfort, loss of appetite
- Feeling of filling up quickly during meals due to enlarged spleen
- Itching, worse after baths or showers (aquagenic pruritis)
- Muscle, joint or bone pain
- Weight loss
- Anaemia (too few red blood cells)

Diagnosis

The diagnosis of MF is based on the 2016 World Health Organisation (WHO) criteria which include clinical and laboratory features.

A diagnosis of MF requires:

- Three of the major WHO criteria
- At least one minor WHO criterion, present on two consecutive occasions

Major criteria

Rapid increase of abnormal megakaryocytes (large bone marrow cell responsible for the production of platelets), together with the presence of reticulin and/or collagen fibrosis. Reticulin is a type of fibre in connective tissue composed of a specialised collagen (type III). Reticular fibres crosslink to form a fine meshwork in the bone marrow.

Presence of the JAK2, CALR, or MPL mutations, or in the absence of these mutations, presence of another clonal marker.

Not meeting the WHO criteria for any of the following conditions:

- ET
- PV
- Chronic myeloid leukaemia
- Myelodysplastic syndromes or

other myeloid neoplasms

Absence of reactive MF which is caused by infection, an autoimmune disorder, or other chronic inflammatory conditions.

Minor criteria

Anaemia not caused by another condition.

White blood cell count greater than $11.0x10^9/L$.

Enlarged spleen which can be felt on physical examination.

Levels of the enzyme lactate dehydrogenase (LDH) increased above the upper normal limit (approximately 300 international units per litre). LDH is required to turn sugar into energy for the cells of the body.

Presence of immature cells of myeloid origin and nucleated red cells in the circulating blood, with or without anaemia.

Tests used to diagnose MPNs and monitor treatment

All MPNs are diagnosed and monitored using the following tests:

- **Blood tests** – A full blood count measures the number of red cells, different types of white cells and platelets in the blood.
- **Bone marrow sample** – Usually taken from the hip bone under local anaesthetic, using special biopsy needles: Aspirate needle for liquid bone marrow (aspirate) or Trephine needle for 1-2 cm core of bone marrow tissue (biopsy). Bone marrow samples can identify abnormal blood stem cells to confirm the MPN diagnosis.
- **Gene mutation analysis** – Blood tests may be performed to check for mutations in the patient's genes. The presence of genes such as JAK2, CALR and MPL are helpful for the diagnosis of the MPN. In addition, next generation gene sequencing and cytogenetics will help provide information to determine the prognosis.
- **Abdominal ultrasound scan** – Often it will be easy to feel an enlarged spleen, however an ultrasound is done in patients where the spleen is less enlarged. This will also help to look for liver enlargement or abnormalities of other organs.

Goals of treatment in MPNs

For patients who have no symptoms, a 'watch and wait' approach, involving regular check-ups and blood tests, but no active treatment, is often recommended.

Treatment of MPNs are guided by patients' risk for thrombosis and any particularly bothersome symptoms such as anaemia or an enlarged spleen. Thrombosis and haemorrhage result in lasting symptoms and shorten survival.

Managing the symptoms of MPN patients and preventing associated problems, particularly thrombotic and haemorrhagic complications, is very important.

- Around 33% of MPN patients suffer from arterial or venous thromboembolism with deep vein thrombosis being the most common event, followed by cardiac events.
- Patients with MPNs commonly have more unusual sites of venous thrombosis such as splanchnic vein thrombosis and cerebral vein thrombosis. The splanchnic venous circulation drains the blood from the stomach, pancreas, spleen and the intestines, and the cerebral vein drains blood from the brain.

Reducing the number of cells (cytoreductive treatment) is used to lower the production of blood cells and help maintain a normal blood volume.

- Procedures include phlebotomy (venesection) or plateletpheresis (removal of excess of platelets from the blood).
- In addition, there are a number of medications such as ruxolitinib, interferon or hydroxyurea available.

Regular monitoring of symptoms and test results will help track any progression of the MPNs and the efficacy of treatment.

Thrombosis risk categories for MPNs

Thrombosis risk categories for patients with PV and ET

For patients with PV and ET, the thrombosis risk categories are shown in the following table:

MPN	Thrombosis risk category	Risk factors
PV	High	Age over 65 years or history of thrombosis
PV	Low	Neither of the above criteria are present
ET	High	Age over 60 years with JAK2 mutation or history of thrombosis
ET	Intermediate	Age over 60 years, no history of thrombosis and no JAK2 mutation
ET	Low	60 years or less, no history of thrombosis but JAK2 mutation present
ET	Very low	60 years or less, no history of thrombosis and no JAK2 mutation

The JAK2 mutation is considered as a thrombotic risk for PV and ET.

Additional risk factors in patients with PV and ET include:

- A very high platelet count
- Smoking, high blood pressure and/or cholesterol, and diabetes

Thrombosis risk categories for patients with MF

Thrombotic risks for patients with MF are numerous and include:

- Haemoglobin <10 g/dL
- White blood cells >25x10^9/L

- Platelets <100x10^9/L
- Circulating abnormal cells ≥2%
- Bone marrow fibrosis grade ≥2
- Clinical symptoms (fatigue, sweating, fever, enlargement of the spleen, etc)
- High-risk mutations:
    - ASXL1 (Additional Sex Combs Like-1)
    - SRSF2 (Serine and Arginine Rich Splicing Factor 2)
    - EZH2 (Enhancer of zeste homolog 2)
    - IDH1 (Isocitrate dehydrogenase 1)
    - IDH2 (Isocitrate dehydrogenase 2)
    - Absence of CALR type-1 mutation Prognostic risk categories for MPNs

Prognostic risk categories for MPNs are slightly different to their thrombosis risk categories detailed above, although they do have common elements such as age thrombosis risk factors, particularly for PV and ET.

Prognostic risk categories for PV and ET

Prognostic risk factors for PV and ET patients focus on patient age and likelihood of thrombosis. Platelet count is also a prognostic risk factor for ET.

The conventional European LeukemiaNet prognostic scoring systems for PV and ET therefore includes the risk factors of age and previous experience of thrombosis, with platelet count also being incorporated for the ET prognostic scoring system.

Other prognostic scoring systems are available, however, at present they are not widely used in clinical practice at present.

Thrombosis risk categories for MPNs (cont.)

The European LeukemiaNet prognostic scoring systems for PV and ET are shown in the following table:

European LeukemiaNet prognostic scoring systems	Risk factors	Risk categories
PV	Age ≥60 years Previous thrombosis	**Low risk** • Age <60 years **and** • No history of thrombosis **High risk** • Age ≥60 years **and/or** • History of thrombosis
ET	Age ≥60 years Previous thrombosis or major bleeding Platelet count ≥1500x10^9/L	**Low risk** • Age <60 years **and** • No history of thrombosis or major bleeding **and** • Platelet count <1500x10^9/L **High risk** • Age ≥60 years **and/or** • History of thrombosis or major bleeding **and/or** • Platelet count ≥1500x10^9/L

Prognostic risk categories for MF

Prognostic risk factors for MF patients include thrombosis risk factors, given the impact of thrombosis on patient survival, and genetic mutations which affect overall survival.

These prognostic risk factors are incorporated into prognostic scoring systems. Current MF prognostic scoring systems include:

- MIPSS70 (Mutation-enhanced International Prognostic Scoring System developed for transplant-age patients ≤70 years of age). Incorporates genetic mutation risks.
- MIPSS70+ includes the same mutations as MIPSS70, with the addition of the U2AF1 mutation, but only 3 clinical risk factors.
- MIPSS70+ version 2.0 includes five genetic and four clinical variables and enables further refinement of the MIPSS70+ low-risk group into very low risk and low risk categories. MIPPS70+ version 2.0. It also permits identification of patients in the MIPSS70+ high-risk category to be reassigned to the very-high-risk category.

Thrombosis risk categories for MPNs (cont.)

Prognostic scoring system **Risk factors**	**MIPSS70 [points assigned]**	**MPISS70+ [points assigned]**	**MPISS70 + version 2.0 [points assigned]**
Haemoglobin <10g/dL	Present [1]	Present* [1]	Present* Moderate anaemia [1] Severe anaemia [2]
White blood cells >25 109/L	Present [2]	-	-
Platelets <100 109/L	Present [2]	-	-
Circulating abnormal cells ≥2%	Present [1]	Present [1]	Present [1]
Clinical symptoms	Present [1]	Present [1]	Present [2]
Bone marrow fibrosis grade ≥2	Present [1]	-	-
High-risk mutation: ASXL1, SRSF2, EZH2 and IDH1/2	Present [1]	Present [1]	Present [4]
≥2 high-risk mutations	Present [2]	Present [2]	Present [2] for ≥1 high-risk mutations [3] for ≥2 high-risk mutations
Low-risk CALR type-1 mutation	Absent [1]	Absent [2]	Absent [2]
U2AF1 mutation	-	Present [3]	Present [3]

*Sex-specific haemoglobin thresholds defined as severe: men <9g/dL and women <8g/dL; moderate: men 9-10.9 g/dL and women 8–9.9 g/dL

MIPSS70 risk factors are combined to create 3 risk categories:

- Low-risk: 0–1 points
- Intermediate-risk: 2–4 points
- High-risk: ≥5 points

MIPSS70+ risks factors are combined to create 4 risk categories:

- Low-risk: 0–2 points
- Intermediate-risk: 3 points
- High-risk: 4–6 points
- Very high-risk: ≥7 points

MIPSS70+ version 2.0 risk factors are combined to create 5 risk categories:

- Very low-risk: 0 points
- Low-risk: 1-2 points
- Intermediate-risk: 3-4 points
- High-risk: 5–8 points
- Very high-risk: ≥9 points

Management of thrombosis

Treatment of PV and ET is usually based on an assessment of the patients' risk factors for blood clots or bleeding. While cytoreductive therapy is a fundamental part of treatment, managing any potential blood clots or bleeding is equally important.

Aspirin

In patients with PV and ET, daily low dose aspirin is usually prescribed. In addition to reducing pain and lowering temperature, aspirin prevents platelets sticking together and may reduce the risk of developing a blood clot, especially for patients with a history of blood clots.

Low-dose aspirin in patients with PV and ET reduces the risk of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis and death from cardiovascular causes.

Side effects of low-dose aspirin

Thrombosis risk categories for MPNs (cont.)

are bruising, bleeding, and indigestion caused by gastric irritation, ulcers and bleeding in the stomach.

Anticoagulation treatment

Long-term anticoagulation treatment can be started for patients with a venous thromboembolism that has occurred with no identifiable risk factor. This will be done after the patient's bleeding risk has been assessed.

The use of anticoagulants will be carefully monitored to balance the increased risk of bleeding with the need to prevent recurrence of thrombosis.

Management of haemorrhage

Haemorrhage is a less common complication of MPNs than thrombosis, occurring in less than 10% of patients. However, it can still affect the mucous membranes, gastrointestinal tract and skin of patients with MPNs.

Long term risk of haemorrhage is usually reduced by controlling the blood cell counts

Significant bleeding episodes are managed with tranexamic acid (anti-fibrinolytic drug that helps the natural blood-clotting process) that stops the fibrin from being broken down. This helps blood clots stay in place where they are needed, which can stop bleeding in the short term, or a transfusion of platelets.

Treatments for MPNs

Treatment options for all MPNs

Treatment for MPNs is driven by the patient's risk for thrombotic complications and any particularly bothersome symptoms such as anaemia or an enlarged spleen (Harrison 2016).

In general, treatment options for patients with MPNs include:

Cytoreduction

Some MPN patients, particularly those at low-risk or intermediate-risk of thrombosis, may not need cytoreduction and can be managed with a Watch and Wait approach and aspirin.

Cytoreductive treatment is useful for treating MPN patients at risk of thrombosis as it allows blood cell counts to be regulated and is the only treatment that significantly reduces the occurrence of blood clots.

Cytoreductive medications

Hydroxycarbamide (also known as hydroxyurea)

Most commonly used chemotherapy drug to decrease blood cell counts, and mainly used to treat PV and ET.

Superior to anagrelide for reducing blood clots or bleeding in patients with high-risk ET.

Can cause the following mild side effects:

- Increased risk of infection, bruising or mild bleeding, and anaemia
- Fatigue and diarrhoea/ constipation
- Lowering of fertility and harm the developing foetus (effective contraception is recommended while taking it and for a few months afterwards)
- Painful mouth and leg ulcers that can be difficult to treat and require stopping treatment.
- Skin cancer has been reported

Treatments for MPNs (cont.)

in patients receiving long-term hydroxycarbamide. Patients should be advised to protect skin from sun exposure and regularly monitor their skin.

When taken over a long period of time, either alone or in combination with other chemotherapy, it may increase the chance of developing AML.

Cytoreductive procedures

Phlebotomy

Removal of blood from a vein taken at regular intervals to reduce the haematocrit to less than 45% within a period of weeks to months.

Plateletpheresis

Although rarely performed, this short-term procedure, that filters platelets out of the blood with the aim of lowering the platelet count, can be used in patients with extremely high platelet counts and thrombocytosis (i.e., a platelet count >450x10^9/l) to prevent serious clot formation in the brain. Plateletpheresis can be repeated as required.

Interferon alpha

Interferon alpha is a substance which occurs naturally in the body and reduces the rate at which all blood cells are made in the bone marrow.

When formulated into a medicine, it can be given subcutaneously.

In pegylated interferon alpha-2a, a polyethylene glycol compound is attached to the interferon alpha drug which slows the breakdown of the drug in the body, enabling it to act for a longer period and have less side effects.

Side effects include flu-like symptoms, headaches, vision disturbances, depression, liver disease and thyroid disease.

It does not increase the risk of developing into AML.

This can be used in pregnancy.

JAK2 inhibitors

In patients with MPNs and other cancers such as lymphomas and breast cancer, JAK2 inhibitors block the JAK enzymes that send too many signals for the production and growth of cells.

The JAK2 gene makes a JAK2 protein, which stimulates cell growth, but also helps control the number of cells produced. The JAK2 protein is involved in cell cycle progression, cell death and genetic instability. By influencing these functions, JAK2 can determine whether a cell remains benign or becomes malignant.

For MPNs patients who have a JAK2 V617F mutation, the JAK2 protein is constantly switched "on", leading to uncontrolled blood cell production. However, the JAK2 V617F mutation is not required for patients with MPNs to benefit from treatment with JAK inhibitors.

Ruxolitinib (Jakavi, Novartis Europharm Limited) is the first JAK1 and JAK2 inhibitor and works by blocking the JAK enzymes that send too many signals for the production and growth of cells.

Ruxolitinib is currently approved for the treatment of:

- Patients with PV vera who are resistant to or intolerant of hydroxycarbamide. However, it has not been approved by NICE, so it cannot be routinely prescribed in England.
- Patients with an enlarged spleen or symptoms in primary MF, or secondary MF following PV or ET and is recommended by the National Institute for Health and Care Excellence.

In patients with MF, ruxolitinib does not modify the disease process or prevent the risk of transformation to AML, although it can lessen the symptoms of MF and prolong patient survival.

Side effects of ruxolitinib in patients with MF include:

- Reduced red blood cell counts (anaemia)
- Reduced white cell counts, reduced platelet counts
- Increased risk of infections such as shingles, hepatitis B reactivation and tuberculosis

Ruxolitinib 'withdrawal syndrome' involves an acute recurrence of symptoms, an accelerated increase in the size of the spleen, worsening of low blood cell counts, and a septic shock-type

Treatments for MPNs (cont.)

syndrome caused with a drop in blood pressure.Unless abrupt discontinuation is required, gradual tapering of the dose of ruxolitinib should be considered, although the utility of the tapering is unproven.

There is no evidence that treatment with ruxolitinib is likely to cause transformation of PV to MF or AML.

Anagrelide

Anagrelide is a drug that prevents the maturation of platelets and is used to counter the overproduction of platelets, particularly in PV and ET. It also has some effect on the red blood cells.

Anagrelide is approved for the reduction of elevated platelet counts in at risk patients with ET who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy.

Side effects with anagrelide treatment include headaches, palpitations and fluid retention.

It is not suitable for pregnant women and is used with caution for people with heart disease.

Anagrelide is known to increase the risk of PV and ET progressing to MF compared with other cytoreductive therapies.

Treatment for individual MPNs

Treatments for PV and ET

Cytoreduction

Hydroxycarbamide is the chemotherapy most commonly used to treat PV and ET.

For high-risk PV, either pegylated interferon or hydroxycarbamide are considered as first-line treatments.

In patients with ET, hydroxycarbamide is the first-line treatment and the recently being approved anagrelide is considered as second-line treatment.

In addition to cytoreduction, the following treatments may be considered in patients with symptomatic splenomegaly that is resistant to drug treatment:

Splenectomy

Removal of the spleen performed when drug treatment has been unsuccessful and/or in the presence of either severe abdominal pain or excruciating pain related to other body organs (vertebral column, lymph nodes or pleura) trying to make red blood cells to compensate for the bone marrow.

Significant morbidity and mortality is associated with splenectomy. Potential risks and benefits need to be discussed with patients.

Radiotherapy

Radiotherapy of the spleen is an option if splenectomy is not a viable solution, but is rarely used.

It helps to reduce the size of the spleen, and can also relieve other related symptoms, such as bone pain.

Radiotherapy provides temporary relief for between 3 and 6 months; however it may also result in prolonged episodes of anaemia, as well as lowering of the platelet and other white blood cell counts.

Treatments for MF

Based on their prognostic score risk, treatments recommended for patients with MF include:

- **Low-risk MF:** For patients with low-risk MF with no symptoms at diagnosis (score 0) the

Treatment for individual MPNs (cont.)

'watch and wait' approach is recommended.

- **Low-to-intermediate-1 risk MF:** In patients with low-to-intermediate-1 risk MF, ruxolitinib can relieve symptoms of MF and reduce the size of the spleen but, cannot reverse bone marrow fibrosis.
- **Intermediate-2 or high-risk MF:** These patients have the option of an allogeneic stem cell transplant (ASCT) which involves transplantation of bone marrow stem cells from a suitable matching donor such as a sibling, unrelated donor, parent or child.
- For patients with high-risk mutations at diagnosis, an ASCT should be encouraged sooner rather than later, as these mutations are associated with a poor long-term prognosis.

ASCT

ASCT is reserved for patients with intermediate-2-risk or high-risk MF patients due to associated morbidity and mortality.

ASCT is suitable for young patients and patients up to 70 years of age who can withstand the intensive chemotherapy required to prepare the bone marrow to receive the donor's cells.

Data from the European Society for Blood and Marrow Transplantation shows the cumulative incidence of deaths among patients receiving and ASCT was 51.23%, of which 23.10% was due to relapse.

JAK mutation inhibitors

Patients with MF may benefit from targeted chemotherapy with a JAK mutation inhibitor such ruxolitinib.

Additionally, patients with MF may require a combination of ruxolitinib and cytoreductive treatments. Managing symptoms of MF can also be achieved with ruxolitinib, interferon or hydroxyurea.

Ruxolitinib and cytoreductive treatments can decrease the symptoms, particularly reducing the size of the spleen, improving

quality of life, and prolonging survival in patients responding to ruxolitinib. However, they cannot modify MF symptoms.Some MF symptoms may persist despite treatment, but worsening of symptoms usually means that the MF is becoming resistant to treatment.

New treatments in development

Second-generation JAK inhibitors

Second-generation JAK inhibitors that do not suppress the production of normal red blood cells and platelets, as ruxolitinib does, are being developed for use in patients with anaemia and low platelet levels.

- Three of these second-generation JAK inhibitors (pacritinib, momelotinib and fedratinib), all of which inhibit JAK2, are being evaluated in clinical trials.
- Fedratinib is approved in the United States for the treatment of patients with intermediate-2 or high-risk MF, and MF secondary to PV and ET including patients previously treated with ruxolitinib, but it is not yet approved in the United Kingdom.

Histone deacetylase inhibitors

Histone deacetylase inhibitors such as vorinostat and givinostat inhibit the production of cells with the JAK2 V617F mutation.

Vorinostat has been shown to achieve a response in 35% of patients with ET, but it had unpleasant side effects which limits its use (Andersen et al 2013).

Histone deacetylase inhibitors still need further research for the treatment of patients' with ET before they can be fully approved.

Imetelstat

This telomerase inhibitor blocks the telomerase enzyme involved in regulating cell growth and division. By stopping the uncontrolled division of abnormal immature blood cells, it slows the progression of MF.

When given every three weeks to patients with MF, it results in good symptom response and improved overall survival.

Larger studies are needed to confirm this finding, as well as studies of imetelstat in patients with other MPNs.

PRM-151

PRM-151 is a genetically modified version of a protein called pentraxin-2 that was developed to prevent and reduce fibrosis in the treatment of various fibrotic diseases.

In patients with MF, PRM-151 reduces symptoms, decreases the size of the spleen and increases haemoglobin and platelet levels.

A clinical trial comparing PRM-151 with ruxolitinib in patients with MF is ongoing.

Other treatment

New treatments which are also used for managing MPNs include:

- Navitoclax
- Bromodomain Extra Terminal (BET) inhibitors
- Erythropoietin
- Combination of treatments

Role of the haematology clinical nurse specialist

- Acts as key worker for patients and a point of contact offering ongoing support and advice for a variety of symptoms, treatments and side effects
- Collaborates with the haematology Multi-Disciplinary Team to develop and implement strategies for patients
- Represents the patient in Multi-Disciplinary Team meetings with specialist haematology pathologists, radiologists specialising in haematological cancer and nursing staff to discuss treatment options
- Feedbacks information from Multi-Disciplinary Team meetings to patients if they would like to know
- Provides specialist nursing advice for patients in partnership with other haematology health professionals involved in patient care to create a seamless patient journey
- Delivers pre-agreed protocols and influences haematological practice by sharing knowledge with colleagues
- Helps patients to manage their fatigue which is the most reported and severe symptom by patients with MPN and that which patients would most like to find a solution to
- Organises psychological, spiritual, financial and social support for the patient
- Empowers patients to take care of their own health and wellbeing by offering advice, information and support

Assessment of the symptom burden of MPNs

- The symptom burden of MPNs can be assessed using validated symptom assessment tools, such as the Myeloproliferative Neoplasms Symptom Assessment Form Total Symptom Score (MPN-SAF) TSS or its abbreviated form MPN-10, which assesses only the 10 most prominent symptoms among patients with MPNs - fatigue, concentration problems, early

satiety, inactivity, night sweats, pruritus, bone pain, abdominal discomfort, weight loss and fever.

- Compared with the general population, MPN patients experience a significant burden of symptoms highlighting the need for effective management of symptoms. However some patients do not always recognise symptoms associated with their MPN.
- Symptom burden of MPNs have an impact on patients' work and productivity, as well as an emotional burden.
- Studies show that patients can experience symptom burden even when their blood counts are controlled.
- A detailed history of the patient's symptoms at diagnosis is useful to be able to monitor the progression of symptoms and the development of any side effects each time the patient is seen by the clinical nurse specialist.
- Quality of life and symptom questionnaires can help patients focus on their symptoms instead of dismissing what has now become normal for them
- Regular monitoring of symptoms will help track any progression of MPNs and the efficacy of treatment.

Management of symptoms and side effects of treatment

Anaemia

- Anaemia in patients with MPNs can be either a symptom of the MPNs or a side effect of treatment. Anaemia may also be due to bone marrow failure or bleeding.
- Signs and symptoms of some MPNs may be anaemia and/or an enlarged spleen with symptoms such as fatigue, fever, weakness, sweats, shortness of breath, bone pain, and fibrosis of the bone marrow (MF only).
- Anaemia may be a side effect of treatment, particularly

Role of the haematology clinical nurse specialist (cont.)

hydroxycarboxamide or ruxolitinib. For patients on ruxolitinib, the dose may need adjusting, particularly for those patients who already have anaemia.

Treatment of anaemia, which occurs more commonly in MF, can include:

- Blood transfusion involving the transfer of red blood cells from a compatible donor to the patient. This will quickly raise the red blood cell count and reduce symptoms of anaemia, often within 24-hours.
- Drugs that may improve anaemia in patients with MF include interferons such as interferon-alpha, immunomodulatory drugs such as thalidomide, steroids such as prednisolone, and androgens such as danazol.
- Danazol is a semi-synthetic androgen hormone which has been shown to improve anaemia in 30% of patients. However, its use is often limited by its side effects of weight gain, male pattern hair growth and toxic effects on the liver. It is important to regularly monitor patients on danazol using liver tests, as well as screen for liver cancer, and prostate cancer in men.
- Erythropoietin, which is a growth factor protein normally made in the kidney, will stimulate the bone marrow to make red blood cells. It has been developed in the laboratory as a medicine to treat anaemia in a range of diseases. It is used mainly in MF, but is of limited value in patients dependent on transfusions and may make an enlarged spleen in patients worse.

Follow-up

- Patients with MPNs will require long-term follow-up, irrespective of whether they are on or off treatment.
- It is often shared between haematologists and clinical nurse specialists and general practitioners. The haematology healthcare team works with patients to decide on the appropriate follow-up care which is coordinated by the haematology clinical nurse specialist.

Abbreviations

AML

Acute myeloid leukaemia

ASCT

Allogeneic stem cell transplant

ASXL1

Additional Sex Combs Like-1

BCR-ABL1

Breakpoint Cluster Region-Abelson murine leukaemia 1, also called Philadelphia chromosome

BET

Bromodomain Extra Terminal

CALR

Calreticulin

ET

Essential thrombocythaemia

EZH2

Enhancer of zeste homolog 2)

IDH1

Isocitrate dehydrogenase 1

IDH2

Isocitrate dehydrogenase 2

JAK2

Janus Kinase 2

LDH

Lactate dehydrogenase

MF

Myelofibrosis

MIPSS70

Mutation-enhanced International Prognostic Scoring System developed for transplant-aged patients ≤70 years of age

MIPSS70+

MIPSS70 which includes a two-tiered cytogenetic risk variable

MPL

Myeloproliferative Leukaemia virus gene MPL515L/K

MPN

Myeloproliferative neoplasm

MPN-SAF TSS

Myeloproliferative Neoplasms Symptom Assessment Form Total Symptom Score

PV

Polycythaemia vera

SRSF2

Serine and arginine Rich Splicing Factor 2

WHO

World Health Organisation

Leukaemia Care is a national charity dedicated to providing information, advice and support to anyone affected by a blood cancer.

Around 34,000 new cases of blood cancer are diagnosed in the UK each year. We are here to support you, whether you're a patient, carer or family member.

Want to talk?

Helpline: **08088 010 444**
(free from landlines and all major mobile networks)

Office Line: **01905 755977**

www.leukaemiacare.org.uk

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