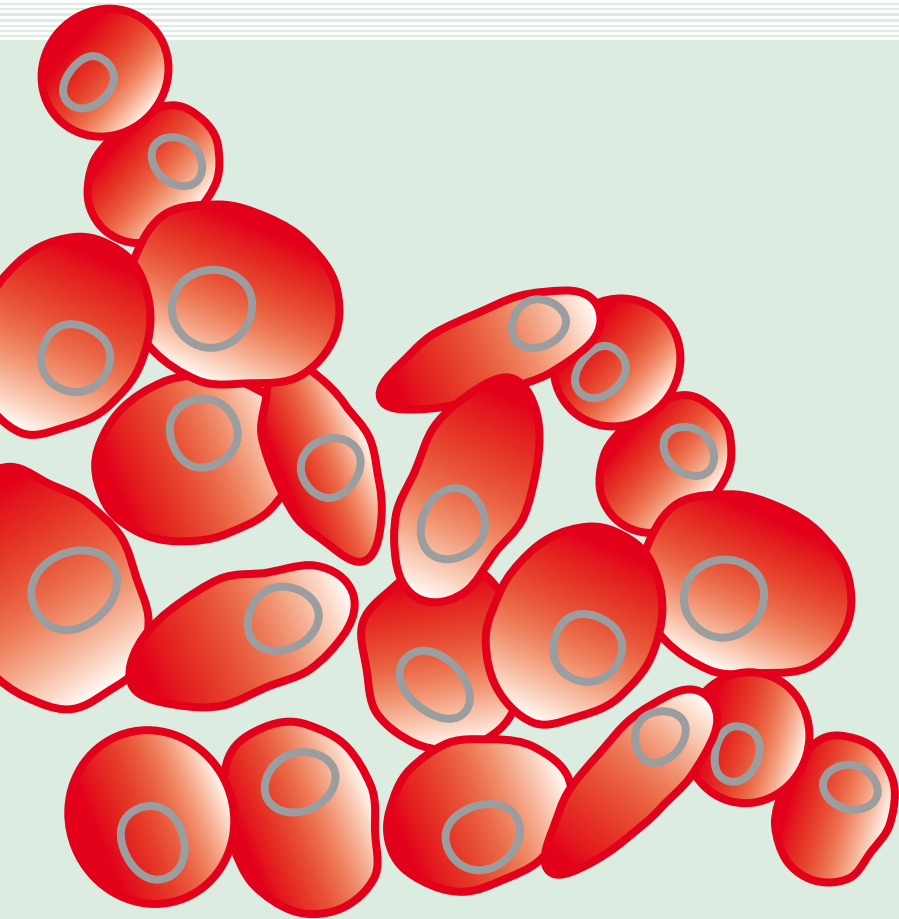


Myeloproliferative Disorders (MPD)



The diagnosis of a blood cancer can be a devastating event for patients, families and friends. It is therefore vital for everyone to have access to reputable and understandable information to help cope with the illness. Whenever possible our booklets are written in line with national guidelines for the treatment of patients with a blood cancer. The information in our booklets is more detailed than in many others but is written in a clear style with all scientific terms explained for the general reader.

We recognise that the amount and level of information needed is a personal decision and can change over time. Particularly at the time of diagnosis, patients may prefer less detailed information. A number of alternative sources of information are available which complement our publications.

The booklets in this series are intended to provide general information about the topics they describe. In many cases the treatment of individual patients will differ from that described in the booklets.

At all times patients should rely on the advice of their specialist who is the only person with full information about their diagnosis and medical history.

For further advice contact the clinical information team on 020 7269 9060.

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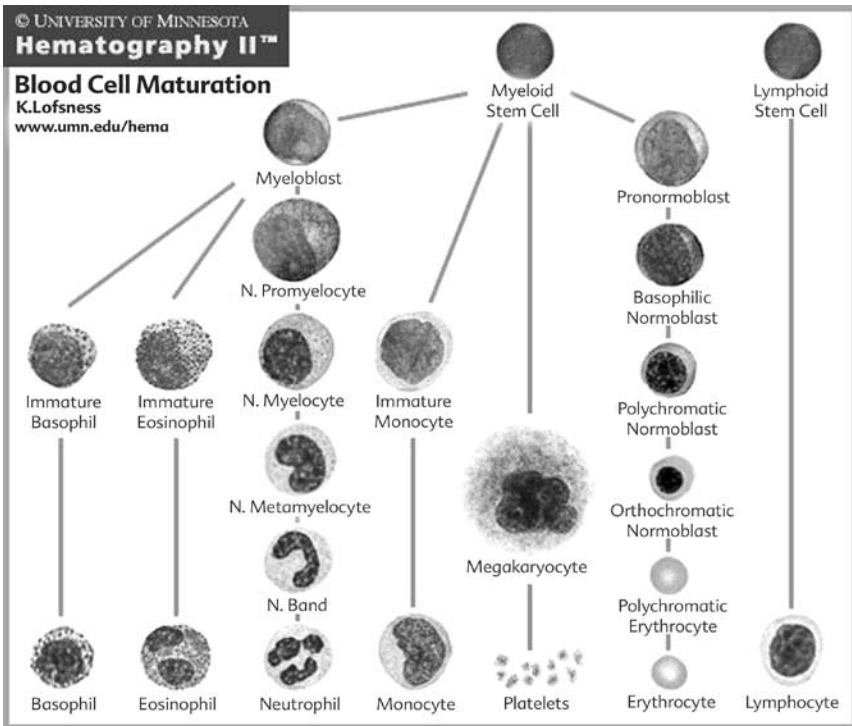
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The myeloproliferative disorders

The myeloproliferative disorders are a group of conditions closely related to leukaemia in which there is excess production of one or more type of blood cell in the bone marrow. There are three main types called essential thrombocythaemia, polycythaemia vera and myelofibrosis. Some doctors include chronic myeloid leukaemia within this category but it is more usual to treat this as a separate disorder.



Origin of the different types of the blood cells from bone marrow stem cells

All blood cells are produced within the bone marrow. To sustain the necessary levels of blood cells the bone marrow of an adult must produce about three million red cells and 120,000 white cells every second. Blood cells are produced from very primitive cells called stem cells. Less than 1 in 5,000 of the marrow cells is a stem cell. As well as producing mature blood cells, stem cells have the remarkable ability to reproduce themselves. This maintains the pool of blood forming stem cells throughout life. Both the production of blood cells and maintenance of the correct numbers of each type of blood cell are controlled by chemicals called growth factors or cytokines.

The normal marrow produces three types of blood cell – red cells, platelets and white cells. Red blood cells contain haemoglobin which carries oxygen to the body tissues. A lack of haemoglobin is called anaemia which will cause fatigue after gentle exercise, general weakness and shortness of breath. Red blood cells survive for about four months from the time they are produced in the bone marrow. Their production is stimulated by a hormone called erythropoietin, levels of which normally increase in response to reduced oxygen content of the blood.

Platelets circulate in the blood and are important in the early stages of forming a blood clot to prevent continued bleeding after an injury. A shortage of platelets can cause bruising and bleeding from minor wounds and from the gut, mouth and other sites. Platelets live for a matter of days in the circulation.

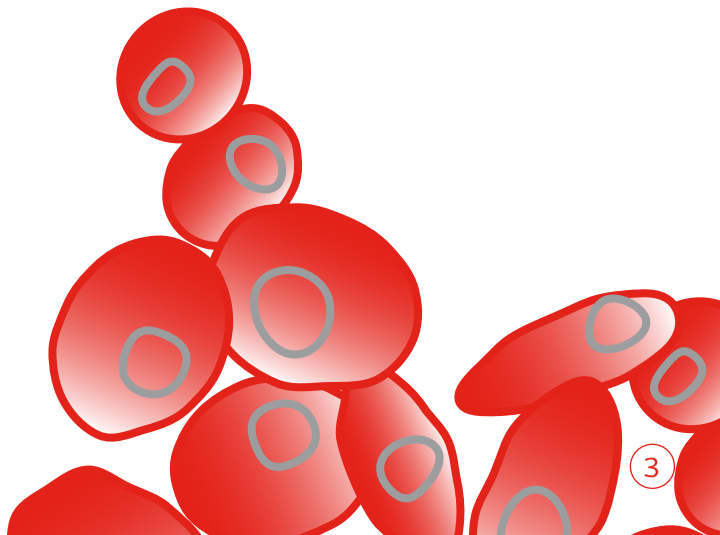
White cells are vital components of the body's immune system – its defence against invading organisms. There are several different types of white blood cell. Their survival varies, the most common type of white cell, the neutrophil, lives for just a few hours while some specialised lymphocytes live for many years.

What is polycythaemia vera?

Polycythaemia vera comes from Greek words meaning many (poly), cells (cyt) in the blood (haemia) and the Latin word for true (vera). This disease (also called polycythaemia rubra [red] vera) is a myeloproliferative disorder in which the abnormal bone marrow produces too many red blood cells. As a result the blood is thicker than normal and contains increased numbers of red cells. In some patients the numbers of white cells and platelets may also be increased.

The average age at diagnosis is about 60 years with about 95% of patients diagnosed at 40 years or older. The disease is virtually unknown under the age of 15 years and then becomes progressively more common up to about 80 years of age. It is about one and a half times more common in men.

The causes of polycythaemia vera are unknown. There are a number of other conditions which may cause a real or apparent increase in the number of red cells and which may occur at any age, including infancy in some cases.



How is polycythaemia vera diagnosed?

Many patients with polycythaemia vera have no signs or symptoms. However, when the number of red cells or platelets is high, patients have an increased risk of blood clot formation which is especially dangerous if they occur in the brain (causing a stroke) or in the heart (causing a heart attack). More rarely, some patients will bleed more easily than normal.

The increase in red cell numbers, especially if it is very high, makes it difficult for the blood to flow smoothly through the blood vessels. This is known as hyperviscosity and the symptoms include headaches and blurred vision. A patient's skin may appear much redder in colour than normal, this is sometimes called plethora.

An unpleasant, although not dangerous, symptom is itching (also called pruritus). This is often noticed after a hot bath. Gout is another unusual complication of polycythaemia vera and is due to increased production and breakdown of red cells.

Polycythaemia may be diagnosed by a simple blood test. Packed cell volume or PCV is a measurement of the proportion of the blood occupied by the red blood cells. Normal PCV values¹ are 40-54% in males, 35-47% in females. Confirmation of the diagnosis of polycythaemia vera requires additional investigations including a measure of the total number of red cells in the body (red cell mass), further blood tests and an analysis of a bone marrow sample.

It may be necessary to have other investigations such as lung function tests to rule out other possible causes of polycythaemia and confirm that the diagnosis is polycythaemia vera.

¹ Some laboratories express the PCV as litres per litre so a PCV of 45% would be reported as 0.45 l/l.

What are the types of polycythaemia vera?

Polycythaemia can be classified as:

- Absolute polycythaemia (an increase in red cell mass)
 - ✦ polycythaemia vera
 - ✦ secondary polycythaemia
 - ✦ idiopathic erythrocytosis
- Apparent polycythaemia (no increased red cell mass)

Polycythaemia vera is a myeloproliferative condition in which there is an increase in the total number of red cells (red cell mass) in the absence of any obvious cause and with the presence of certain characteristic features.

Secondary polycythaemia is a true increase in the number of red cells (in the absence of features of a myeloproliferative disorder) and which has an identifiable cause. There are numerous possible causes of secondary polycythaemia but these can be grouped into three categories. Firstly, a reduction in the oxygen content of the blood will lead to increased levels of the red cell growth factor erythropoietin which stimulates the marrow to produce more red cells. This is called hypoxic secondary polycythaemia and may occur in response to lung disease, smoking, residence at high altitudes or red cell abnormalities which limit oxygen carrying capacity of the red cells. Secondly, abnormally high levels of erythropoietin may be found in several different types of cancer and some benign tumours. Erythropoietin is produced in the kidney and therefore some forms of non-cancerous kidney disease can lead to increased serum levels.

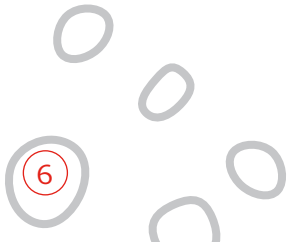
Finally, there is a group of cases of secondary polycythaemia in which erythropoietin levels are normal but there is an increased red cell mass. These cases include new-born infants (in whom polycythaemia is normal), patients treated with certain steroids, when a patient has been overtransfused and a rare condition in which the marrow produces red cells independently of the levels of erythropoietin.

Idiopathic erythrocytosis describes an increase in red cell mass without evidence for a diagnosis of either polycythaemia vera or secondary polycythaemia. This is sometimes called benign erythrocytosis or pure erythrocytosis. Some of these cases may represent either secondary polycythaemia in which the cause remains undetected or polycythaemia vera without typical clinical features.

In apparent or spurious polycythaemia the red cell mass is normal though a reduction in the volume of plasma (the liquid portion of the blood) can make the red cell mass appear raised. The simplest and commonest example of this would be a person who is dehydrated. The reduced volume of plasma will make the blood appear thicker when the total red cell mass is not actually increased. The only treatment required is replacement of fluid.

A packed cell volume of greater than 60% is always indicative of true polycythaemia. Apparent polycythaemia is more common in men than in women and is the most likely explanation for a moderately increased packed cell volume.

Treatment of secondary and apparent polycythaemia is by correction of the underlying cause of the polycythaemia, at which time the blood will return to normal. If this fails to happen further tests are necessary to exclude a hidden diagnosis of polycythaemia vera.



Treatment of polycythaemia vera

Unfortunately there is no treatment which will cure polycythaemia vera. However it can usually be kept under effective control by regular follow-up. Polycythaemia vera can generally be considered a relatively benign disorder which frequently does not interfere significantly with the patient's activity or working life for a long time, if at all.

The recommended treatment for polycythaemia vera depends on the duration/severity of the condition, the age of the patient, and on which type of cell is most affected. The simplest and most rapid way to reduce the number of red cells is blood-letting. This is called venesection or phlebotomy. About one pint (half a litre) is removed at a time and the procedure is repeated as often as necessary.

The aim is to thin the blood so that the PCV is less than 45% in most cases. This may mean taking blood as often as once a week initially. Intervals between bleeding become longer as the patient becomes moderately iron-deficient which tends to keep the PCV lower than it would otherwise be. The main limitation of this treatment is that it does not reduce the platelet count. The principal benefit is that there are virtually no side-effects of the treatment.

If the platelet count is also too high, a more appropriate form of treatment is to use an oral drug such as hydroxyurea or injections of interferon. The major reservation about the use of hydroxyurea is that it may increase the risk that the condition will transform to acute myeloid leukaemia in later life. For this reason hydroxyurea is generally avoided in younger patients (those under 50 years of age). Interferon is not thought to carry this risk but many patients find the short-term side-effects unpleasant and not all patients can tolerate interferon therapy.

Some patients, especially those who have high numbers of platelets, may be at risk of abnormal clotting leading to strokes. The use of small daily doses of aspirin may help to prevent blood clots but it is important that patients do not take any medicine containing aspirin except on the instructions of their specialist. If a painkiller is needed then paracetamol, which does not affect platelets, can safely be used.

A small proportion (less than 10%) of PRV patients may eventually develop acute myeloid leukaemia.² In others the overactive marrow seems to exhaust itself after many years and the condition converts to one called myelofibrosis in which scar tissue develops in the bone marrow.

The major long term side-effect of treatment is the possibility of secondary leukaemia in patients who receive prolonged treatment with hydroxyurea. It must be emphasised that only a small minority of patients develop such leukaemias and patients whose disease is controlled by the effective use of drugs live considerably longer than untreated patients.

Prognosis

Given that many patients are diagnosed in late life, there is a very good chance of patients living a normal life-span if their condition is carefully monitored and treated as necessary. If patients with polycythaemia vera have their condition properly controlled then the median survival is about 15 years post-diagnosis.

NB: Median survival is often misunderstood by patients and family to mean the maximum expected lifespan. In fact, it is the time at which one would expect half of a group of patients diagnosed at the same time to still be alive – many of those still alive will live for many more years, decades even. It is also important to realise that not all patients who die after being diagnosed die from MPD. Particularly in the case of elderly patients, many will die from other diseases. Finally, one should always remember that survival data is historical and may not reflect improvements based on newer drugs or treatments.

² There is a separate publication on acute myeloid leukaemia available from Leukaemia Research.

What is essential thrombocythaemia?

Essential thrombocythaemia is due to an abnormality of platelet producing cells (megakaryocytes) in the bone marrow but the underlying cause is not known. Essential thrombocythaemia is only one of several possible causes of an increased number of platelets in the blood. For example bleeding, inflammation or cancer can cause high platelet counts but these are not essential thrombocythaemia.

The condition is most commonly diagnosed in patients between the ages of 50 and 70 years, though it has been reported (rarely) in children and may occur at any age. Men and women are equally at risk.

The causes of essential thrombocythaemia are unknown.



How is essential thrombocythaemia diagnosed?

Many patients with essential thrombocythaemia have no signs or symptoms and the disease is often detected by chance as a result of a routine blood count. Symptoms are more frequent in older patients and/or when the platelet count is very high. Patients who have no symptoms at the time of diagnosis require regular check-ups and should report any symptoms which may develop to their doctor. The general practitioner will advise on whether they should be referred for further tests or for a specialist appointment to determine whether the condition is progressing.

Any patient who experiences any of the following should see their doctor promptly:

- Persistent or repeated headaches
- Disturbances of vision (described by patients as light shows or silent migraines)
- Dizziness or ringing in the ears
- Bruising or bleeding (including heavy periods or nose bleeds)
- Fullness in the abdomen (may be swollen liver or spleen)
- Erythromelalgia (pain and redness in extremities)
- Itching or other peculiar skin sensations
- Leg pains
- Coldness or blueness of the fingers or toes

It is important to understand that these (or any other symptoms) may be unrelated to the essential thrombocythaemia, but it is important to make your doctor aware of the problems so that he or she can assess them further.

Symptoms may result from blood clots forming within vessels (thrombosis) or, less commonly, bleeding. The results of such blood clots depends on where they occur. They are especially dangerous if they occur in the brain (causing a stroke) or in the heart (causing a heart attack). Loss of blood supply to an organ due to a clot is called ischaemia which is qualified by referring to the site where it occurs so that cardiac ischaemia would involve the heart while cerebral ischaemia involves the brain. If, in a patient with thrombosis, a portion of a clot breaks off and travels through the circulation this is called an embolism. If an embolism becomes lodged in one of the blood vessels of the lung this is called a pulmonary embolism and may be fatal.

Erythromelalgia is a rare disorder characterised by burning pain, warmth and redness of the extremities. There is a primary form of this condition but it may also be seen in the myeloproliferative disorders, most frequently in those with essential thrombocythaemia.

In essential thrombocythaemia there is excessive production of platelets and the number of platelets in the blood is increased, sometimes to many times higher than normal. Essential thrombocythaemia is only diagnosed when other possible causes of a high platelet count have been ruled out. These include bleeding, iron deficiency, inflammatory diseases such as arthritis and cancer. A patient who does not have a normally functioning spleen would be expected to have a high or very high platelet count.

Essential thrombocythaemia is usually suspected following the result of a simple blood test which measures the number of the various types of blood cells. Confirmation of the diagnosis requires several subsequent investigations to exclude other causes of a raised platelet count together with an analysis of a bone marrow sample (proposed criteria for the diagnosis of essential thrombocythaemia are given in the appendix).

The essential factors to be demonstrated in a patient with a raised platelet count are:

- No identifiable cause of secondary thrombocytosis e.g. infection, cancer or other disease
- Normal red cell count (to exclude polycythaemia vera)
- Exclusion of high platelet count due to iron deficiency or chronic bleeding
- No excess of fibrous tissue in the bone marrow (excludes myelofibrosis)
- The Philadelphia chromosome³ is not found in the bone marrow (excludes chronic myeloid leukaemia)

³ This is a chromosome abnormality sometimes seen in the myeloproliferative disorders. It is not an inherited abnormality but is an acquired change only present in the diseased cells. The presence or absence of a Philadelphia chromosome is important both in terms of diagnosis and for monitoring response to treatment.

Risk classification

Essential thrombocythaemia can be categorised as low-, intermediate or high-risk based on a combination of patient features (age, signs and symptoms) and on laboratory findings. The categories, which are described in Appendix A, are of great significance for treatment planning.



Treatment of essential thrombocythaemia

If a patient's condition has been diagnosed as a chance finding then, dependent on their age and on whether they have other signs or symptoms, they may not require any initial treatment. In most cases essential thrombocythaemia can generally be considered a relatively benign disorder which frequently does not interfere significantly with the patient's activity or working life for a long time, if at all. The majority of patients will, however, require some form of treatment.

Treatment may simply be low doses of aspirin, which interferes with the way in which platelets work. Its use in patients with essential thrombocythaemia must be carefully controlled by the doctor. No patient with essential thrombocythaemia should ever take aspirin (or an aspirin containing drug) without being told to do so by the doctor. Patients who have bleeding problems or who have stomach ulcers or known sensitivity to aspirin will be advised not to take this medication.

Paracetamol should be used instead of aspirin if a medicine is needed for pain or fever. If a patient needs to see a doctor other than their regular GP or specialist, they must ensure that the doctor knows that they have essential thrombocythaemia and that aspirin and related drugs must be used with caution.

If a patient has a very high platelet count and symptoms of bleeding or clotting then the count may need to be lowered as quickly as possible. If this cannot be done with hydroxyurea then a special procedure called platelet pheresis will selectively remove the platelets from the blood.

PT-1 Trial

A clinical trial called the MRC PT-1 is comparing treatment options for patients diagnosed with essential thrombocythaemia.⁴

High risk patients in the trial were randomised to receive either hydroxyurea plus aspirin or anagrelide plus aspirin. This section of the trial has now been stopped on the basis of initial results. Compared with patients on hydroxyurea it was found that those receiving anagrelide showed increased rates of arterial thrombosis (clotting), major bleeding and myelofibrosis but less venous thrombosis. More patients receiving anagrelide were unable to tolerate this treatment. These results indicate that hydroxyurea should be first line therapy for ET patients at high risk of thrombosis. However, anagrelide can be useful for patients unable to take hydroxyurea.

Intermediate risk patients have a relatively low risk of thrombosis but if they do develop clots these can be life threatening. Patients in this group will usually receive either aspirin alone (like the low risk group) or aspirin and hydroxyurea. An ongoing section of the PT-1 trial will determine whether hydroxyurea reduces the risk of developing a clot and thus determine whether there is any benefit for this group of patients in adding hydroxyurea to aspirin.

A third section of the PT-1 trial will study patients who are classified as **low risk** and who will receive aspirin alone in order to reduce the risk of clotting (thrombosis). The only exceptions to this are patients who may bleed easily or who have other conditions which prevent the use of aspirin.

Essential thrombocythaemia occurring in pregnancy is very rare and there is little experience of treating these patients, although a management plan has been prepared by the doctors in charge of the anagrelide trial. This will be made available to any doctor caring for a pregnant patient with essential thrombocythaemia.

⁴ There is a separate publication on clinical trials available from Leukaemia Research.

Prognosis

Given that many patients are diagnosed late in life, there is a very good chance of patients living a normal lifespan if their condition is carefully monitored and treated as necessary. If patients with essential thrombocythaemia have their condition properly controlled then the median survival is about 15 years post-diagnosis. A small proportion (less than 10%) of patients may eventually develop acute myeloid leukaemia. In others the overactive marrow seems to exhaust itself after many years and the condition converts to one called myelofibrosis in which scar tissue develops in the bone marrow.

NB: Median survival is often misunderstood by patients and family to mean the maximum expected lifespan. In fact, it is the time at which one would expect half of a group of patients diagnosed at the same time to still be alive – many of those still alive will live for many more years, decades even. It is also important to realise that not all patients who die after being diagnosed die from MPD. Particularly in the case of elderly patients, many will die from other diseases. Finally, one should always remember that survival data is historical and may not reflect improvements based on newer drugs or treatments.

Long-term effects of treatment

The major long term side-effect of essential thrombocythaemia is the possibility of secondary leukaemia developing in patients who receive prolonged treatment with hydroxyurea. It must be emphasised that only a small minority of patients develop such leukaemias and patients whose disease is controlled by the effective use of drugs live considerably longer than untreated patients. This risk, which may develop after many years of treatment, is clearly a more significant influence on treatment choice for younger patients.

What is idiopathic myelofibrosis?

Myelofibrosis (also called agnogenic myeloid metaplasia) is a myeloproliferative disorder in which the bone marrow is initially over-active but then develops scar tissue (fibrosis). The term idiopathic means without known cause and differentiates this form of myelofibrosis from secondary myelofibrosis which may complicate other bone marrow diseases. Normal bone marrow has a very fine network of fibres supporting the blood forming tissues. In myelofibrosis this network is coarsened and thickened so that normal blood cell production is progressively reduced. As a result blood cell production begins to take place in the liver and spleen which become enlarged. These are both tissues which produce blood cells in the embryo but lose this function before birth. The production of blood cells in the liver and spleen is less efficient and so patients frequently develop anaemia.

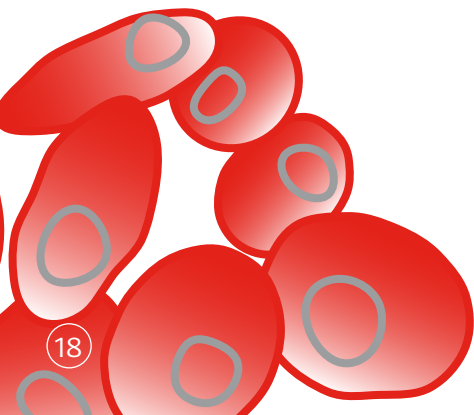
The cells which produce the fibrin network are called fibroblasts. Fibroblasts in the bone marrow of patients with myelofibrosis appear to be normal. Platelet producing cells called megakaryocytes behave abnormally in this condition and stimulate fibroblasts to become overactive, and secrete excessive amounts of fibrous tissue.

The average age at diagnosis is 50-70 years, although myelofibrosis may affect patients of any age. It is particularly rare, although not unknown, in childhood. Men and women are equally at risk. Myelofibrosis may occur in patients who have had either essential thrombocythaemia or polycythaemia vera, or it may develop in patients with no previous history when it is known as primary myelofibrosis.

Myelofibrosis as a myeloproliferative disorder must be distinguished from marrow fibrosis resulting from other diseases such as:

- Spread of cancer to the bone marrow from another site (metastasis)
- Non-Hodgkin's lymphoma
- Hodgkin's lymphoma
- Damage caused by radiation (e.g. radiotherapy for cancer)
- Tuberculosis
- Leishmaniasis (a parasite infestation)
- Other blood diseases (e.g. chronic myeloid leukaemia, acute myeloid leukaemia, myelodysplastic syndrome, myeloma, hairy cell leukaemia)

The causes of the myelofibrosis are unknown. Exposure to either high levels of benzene or of ionizing radiation have been reported to increase the risk of myelofibrosis. However, this would account for only a very small proportion of cases, if any in Britain, mainly arising from occupational exposures. The great majority have no obvious cause.



How is myelofibrosis diagnosed?

About 20% of patients have no symptoms at the time of diagnosis and myelofibrosis is discovered as a chance finding after a routine blood test. The most common symptoms are excessive tiredness or breathlessness because of anaemia or abdominal discomfort due to enlargement of the spleen. Sometimes patients report unexpected weight loss. In later stages of the disease bruising/bleeding may occur due to lack of platelets and repeated and persistent infections may become a problem due to lack of healthy white cells.

A simple blood test to measure the numbers of the various types of blood cells is usually the first step to the diagnosis of myelofibrosis. Red blood cells with characteristically abnormal shapes are highly suggestive of a diagnosis of myelofibrosis. However, confirmation of the diagnosis requires a number of additional investigations and analysis of a bone marrow sample to detect the fibrous tissue. This involves obtaining a small amount of marrow from inside the bone with a needle (a bone marrow aspirate) and a sample from the bone itself to show the structure of the bone marrow cavity (a bone marrow trephine biopsy). In many cases the amount of fibrous tissue will make it impossible to withdraw bone marrow cells using a needle and syringe. This is known as a 'dry tap' and always indicates the need for a trephine biopsy. As mentioned above it is necessary to distinguish myelofibrosis occurring as a disease from excessive fibrosis as a feature of other conditions. A set of criteria have been proposed by a group of experts. These require:

- Presence of an enlarged spleen (splenomegaly)
- Fibrosis affecting more than one-third of the area of an adequate marrow biopsy
- A characteristic blood film (this is called a leukoerythroblastic blood picture)
- Absence of an increased red cell mass (polycythaemia)
- Absence of the Philadelphia chromosome (chronic myeloid leukaemia)
- Exclusion of other diseases causing myelofibrosis

Progression of myelofibrosis

There is a recognised progression of the features of myelofibrosis which gives some indication of how advanced the disease may be and reflects the natural history of the disease.

Initially there is an overactive marrow with increased numbers of megakaryocytes (platelet-producing stem cells) and a slight excess of fibrin. This is known as the cellular phase and may require careful evaluation to distinguish it from leukaemia.

An increase in the amount of fibrosis indicates progression to the fibrotic phase. There is a decrease in the amount of normal blood-forming tissue and the structure of the bone marrow (architecture) is altered.

The sclerotic phase (myelosclerosis) is marked by an increase in the amount and density of the bone within the marrow cavity. There is an even greater disruption of the architecture of the marrow which is shown by the marrow biopsy. There is a very large increase in the amount of fibrotic tissue. In a small proportion of patients increased bone formation becomes the most dominant feature and this is termed osteomyelosclerosis.

Treatment of myelofibrosis

The appropriate choice of treatment for a patient with myelofibrosis will depend on the details of each case. Patients diagnosed by laboratory tests but who do not have severe anaemia and have no clear symptoms, are usually seen regularly in the out-patient clinic but may not need treatment.

Patients who have severe anaemia will require regular blood transfusions, usually every one to three months. These can usually be carried out during a single day without the patient having to stay in hospital overnight.

An enlarged spleen may cause problems by becoming painful. It may also make the anaemia worse by destroying normal blood cells. In such cases the large spleen may be reduced in size by treatment with drugs such as hydroxyurea. Alternatively an operation to remove the spleen (splenectomy) can be helpful.⁵ There are potential complications which may result from splenectomy for patients with myelofibrosis. The decision for or against surgery is made on an individual basis after discussion between the patient and the specialist. Splenectomy may be particularly helpful if patients have a very low platelet count because the spleen normally stores platelets. An enlarged spleen may take up as much as three-quarters of the total number of platelets being released into the bloodstream.

As a temporary measure a patient with a very enlarged spleen may receive local radiation therapy to reduce its size. This is usually only effective for a period of a few months to a year or two after which the spleen usually enlarges again. If this treatment is carried out frequent blood tests are needed because in patients with advanced myelofibrosis the spleen may be carrying out a significant proportion of the body's total blood cell production. When the spleen is removed the blood cell counts may drop initially.

⁵ There is a separate publication on splenectomy available from Leukaemia Research.

Several drugs, including thalidomide and interferon, are being studied to determine their possible value in the treatment of myelofibrosis. In the early stage when blood counts are raised conventional chemotherapy drugs such as hydroxyurea may be of benefit. There have been no specific trials to determine the relative advantages of one chemotherapy drug over another.

Only a minority of patients may be eligible for a donor stem cell transplant⁶ which is the only treatment considered potentially curative of this disease. Unfortunately, most patients with myelofibrosis are too old to be considered for this treatment. The risks associated with a transplant are relatively high but there is evidence that a successful transplant may lead to long-term survival. Younger patients, for whom this may be an option will be given detailed information by their specialist to enable them to make a choice.

The usual management of myelofibrosis is to keep patients comfortable and well without upsetting them with the side-effects of the treatment. In such a chronic condition with such a variable outcome, predictions of how an individual case will develop and what line of treatment should be followed must be determined individually between the patient and their doctor(s).

Prognosis

The course of myelofibrosis is very variable. Some patients have a mild disease which does not progress rapidly. In such cases the condition is relatively benign and need not interfere significantly with the patient's activity and working life. In other cases the disease progresses more quickly and patients become dependent on blood transfusions.

Myelofibrosis will usually cause a significant shortening of life expectancy, except for the minority of younger patients who may be eligible for a stem cell transplant. Possibly as many as a quarter of all patients with myelofibrosis may develop acute myeloid leukaemia. Unfortunately, when this does occur this can be more difficult to treat than typical acute myeloid leukaemia.

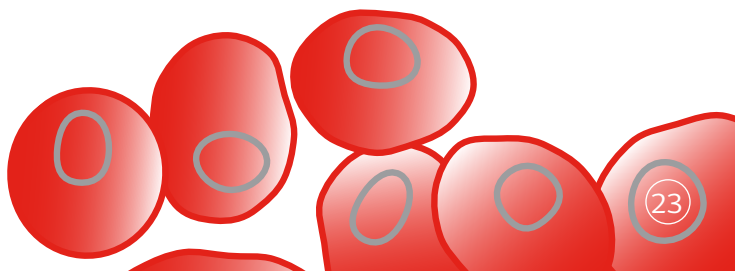
⁶ There is a separate publication on stem cell transplantation available from Leukaemia Research.

Summary

The myeloproliferative disorders are a group of conditions affecting blood-forming stem cells and characterised by overproduction of blood cells usually with one cell line particularly affected. The diseases involved are classified according to the cell type mainly affected as essential thrombocythaemia, polycythaemia vera and myelofibrosis. Essential thrombocythaemia and polycythaemia affect platelets and red cells respectively. In myelofibrosis the main feature is overproduction of fibrous tissue which is a result of normal fibroblasts responding to abnormal control signals from the affected stem cells.

The myeloproliferative disorders are overwhelmingly diseases of late life. Myelofibrosis typically leads to shortening of life expectancy, but the condition is very variable and patients should seek advice on prognosis from their specialist.

Some patients with myeloproliferative disorders will experience transformation of their disease to acute myeloid leukaemia, which may be less responsive to treatment than acute myeloid leukaemia occurring as a primary diagnosis.



Appendix A

Essential thrombocythaemia can be categorised as low-, intermediate- or high-risk based on a combination of patient features (age, signs and symptoms) and on laboratory findings. The categories are of great significance for treatment planning.

For **low risk** disease, **all** of the following features must be present:

- Age less than 40 years
- Platelet count above $600 \times 10^9/l$ but which has never been consistently greater than $1,000 \times 10^9/l$
- No** history of ischaemia, thrombosis or embolic features (including erythromelalgia)
- Absence of haemorrhage considered to be related to essential thrombocythaemia
- Absence of hypertension
- Absence of diabetes

For **intermediate risk** disease, **all** of the following features must be present:

- Age 40-59 years
- Platelet count above $600 \times 10^9/l$ but which has never been consistently greater than $1,000 \times 10^9/l$
- No** history of ischaemia, thrombosis or embolic features (including erythromelalgia)
- Absence of haemorrhage considered to be related to essential thrombocythaemia
- Absence of hypertension
- Absence of diabetes

For **high risk** disease, **any** of the following features is sufficient:

- Age greater than 60 years
- Platelet count greater than $1,000 \times 10^9/l$ (currently or previously)
- History of ischaemia, thrombosis or embolic features (including erythromelalgia)
- Haemorrhage considered to be related to essential thrombocythaemia
- Hypertension or diabetes

A	Diagnostic criteria ET
A 1	Platelet count in excess of $400 \times 10^9/l$ and no known cause of reactive thrombocytosis
A 2	Increase and clusters of enlarged and mature megakaryocytes with hyperdiploid nuclei in bone marrow biopsy material
A 3	No preceding or allied other subtype of myeloproliferative disorders or myelodysplastic syndrome

Proposed Rotterdam Criteria of Essential Thrombocythaemia by the TVSG
J.J. Michiels and E. Juvonen. Sem Thromb Hemostas 1997;23:339-347

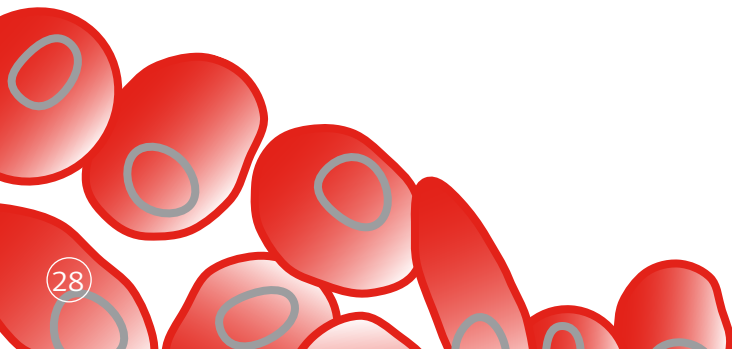
B	Confirmative criteria ET
B 1	Normal or elevated leukocyte alkaline phosphatase score, normal ESR, and no fever
B 2	Normal or increased cellularity of the bone marrow without or with the presence of reticulin fibers in biopsy material
B 3	Splenomegaly on palpation, on isotope or ultrasound scan, or on computer tomogram
B 4	Spontaneous erythroid colony formation (EEC) and/or spontaneous megakaryocyte colony formation (CFU-Meg)

Notes

Notes



Notes



Typical normal values for blood test results

	WBC x 10 ⁹ /l	RBC x 10 ¹² /l	Hb g/dl	ANC x 10 ⁹ /l	Platelets x 10 ⁹ /l
Adult male	3.7 to 9.5	4.3 to 5.7	13.3 to 16.7	1.7 to 6.1	143 to 332
Adult female	3.9 to 11.1	3.9 to 5.0	11.8 to 14.8	1.7 to 6.1	143 to 332
West Indian	2.8 to 9.8			1.0 to 6.5	122 to 374
African	2.8 to 7.8			0.9 to 4.2	115 to 342
Child 2-5 yrs	5 to 13	4.2 to 5.0	11 to 14	1.5 to 8.5	143 to 332
Child 6-9 yrs	4 to 10	4.3 to 5.1	11 to 14	1.5 to 6.0	143 to 332
Child 9-12 yrs	4 to 10	4.3 to 5.1	11.5 to 15.5	1.5 to 6.0	143 to 332

Normal ranges vary slightly between laboratories so you may wish to ask your doctor to enter your normal values below:

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WBC	White blood cell count
RBC	Red blood cell count
Hb	Haemoglobin concentration
ANC	Absolute neutrophil count

Separate ranges are quoted for West Indian and African populations as these groups have different normal ranges for white cell counts, absolute neutrophil counts and platelet counts.

This information is adapted, with permission, from *A Beginner's Guide to Blood Cells*, Dr Barbara Bain. Pub. Blackwell, Oxford, 1996.



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