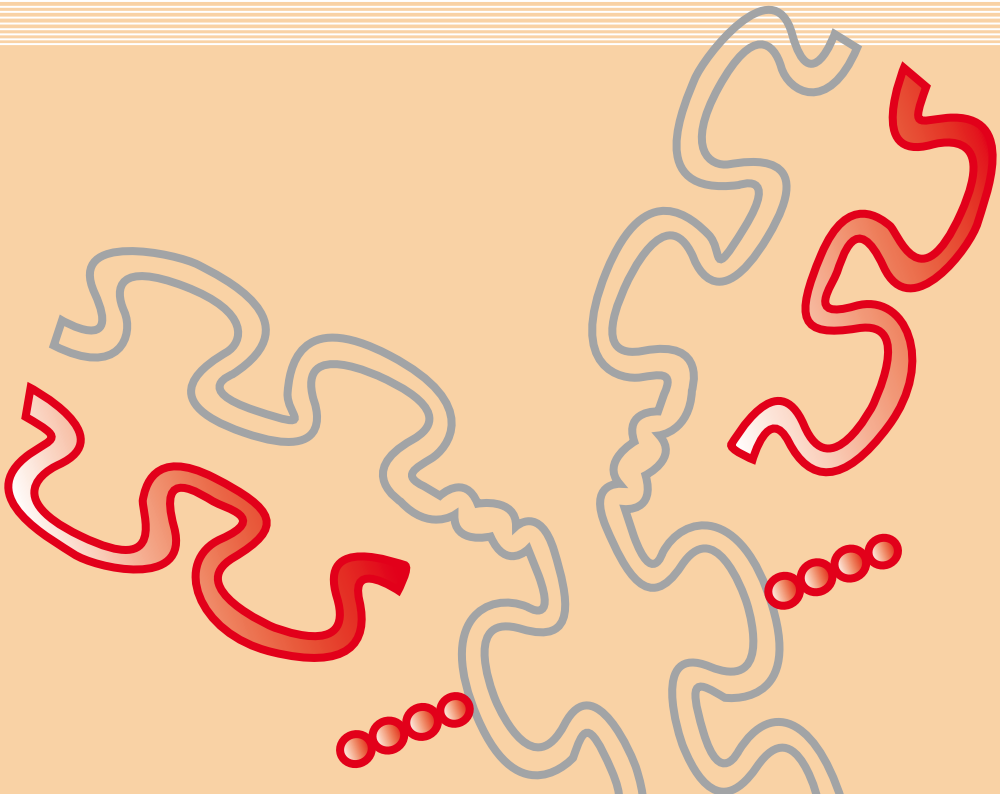


# Multiple Myeloma (MM)



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 diseases 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.**

**Leukaemia Research**

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# What is multiple myeloma?

**Multiple myeloma is a form of cancer which affects plasma cells in the bone marrow. Plasma cells normally produce antibodies and are a specialised form of blood cell called a B lymphocyte. In normal circumstances, the antibody molecules present in the blood are very varied in their structure, reflecting the large number of infections they may be required to combat. In myeloma a single lymphocyte becomes malignant and produces a very large number of identical cells (a clone). In patients with myeloma very large quantities of a single type of antibody are produced. This form of antibody is called paraprotein and it is present in the blood and/or urine in about 99% of cases. Normal antibody levels are almost always reduced in myeloma. This, combined with a slight reduction in the numbers of neutrophils (special type of white blood cell), leads to a susceptibility to infections, which may be life-threatening.**

Detection of a paraprotein alone is not sufficient to give a diagnosis of multiple myeloma, as this may also occur in other conditions including lymphoma, monoclonal gammopathy of unknown significance (MGUS which is described below), amyloidosis<sup>1</sup> and some inflammatory disorders. When paraprotein is not detectable the disease is called non-secretory myeloma.

Bone damage is often the most significant feature of multiple myeloma. The term multiple myeloma refers to the spread of the disease throughout the bone marrow at the time of diagnosis and the presence of multiple sites of affected bone. An altered balance between bone production and destruction leads to areas of thinning of the bone. The 'holes' in the bone which are produced are called lytic lesions. Myeloma cells disturb the balance between

<sup>1</sup> There are separate publications on Hodgkin's disease, non-Hodgkin's lymphoma, monoclonal gammopathy of unknown significance and amyloidosis available from Leukaemia Research.

cells called osteoclasts (which destroy bone) and cells called osteoblasts (which make new bone). Over a period of time this leads to local loss of bone with characteristic abnormalities on X-ray examination and a tendency for bones to break in response to very mild trauma (pathological fractures).

A potentially serious associated problem is hypercalcaemia which is the presence of higher than normal levels of calcium in the blood. Calcium is a major component of bone and the increased breakdown of bone in myeloma leads to the elevated levels in the blood. High blood calcium can cause dehydration and kidney damage which in turn further raises the level of calcium. This vicious circle can be broken by a high fluid intake, often in the range of five to six pints per day.

The diagnosis of multiple myeloma rests on finding excessive numbers of abnormal plasma cells in the bone marrow, abnormal bone appearances on X-rays and the presence of a paraprotein in the blood and/or urine. The disease can be effectively treated with drugs (chemotherapy) and most patients will respond to standard chemotherapy and achieve a state called plateau. In this state patients are free of serious disease symptoms. Plateau phase typically lasts for one to three years. Patients in this phase are not, however, cured as their disease will eventually return - this is called relapse or progression.

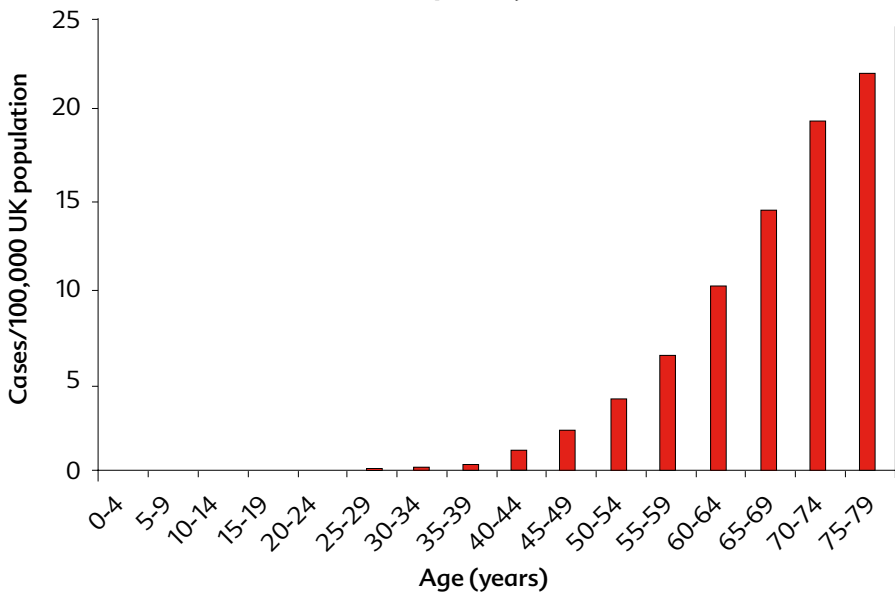


# Who gets multiple myeloma?

**Multiple myeloma is unknown in childhood, very uncommon in young adults and becomes increasingly common with advancing age. Only about 2% of cases in the UK occur in people under the age of 40 years.**

There are about 3,000 new cases each year in the UK. The incidence is about twice as high in males as in females. Multiple myeloma is about twice as common in black people as in white. The reasons for this are not understood but it does imply an underlying variation at the population level in the probability of developing the condition.

**Incidence of multiple myeloma in the UK**



# What are the types of multiple myeloma?

**Myeloma may arise on a background of a clinically benign condition called MGUS. The hallmark of MGUS is the presence of a paraprotein but without evidence of other symptoms or features of myeloma.**

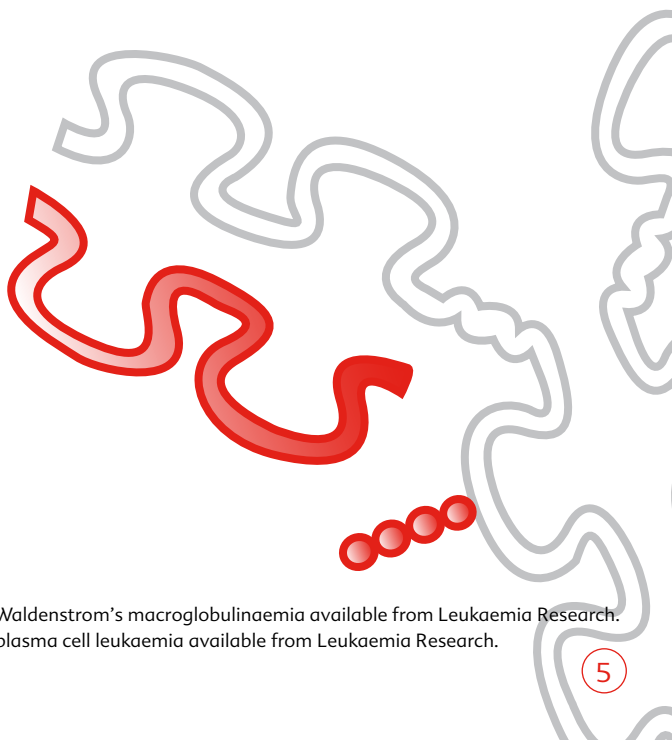
Blood normally contains a large number of different proteins called plasma proteins. About 20% of the total amount of protein in the blood is made up of antibodies produced as part of the body's defences against infection. Collectively they are known as gamma globulins. When most of the protein being produced is one particular form of gamma globulin this is called a monoclonal gammopathy. This means that all of the abnormal protein is identical because it is produced by a population of cells which are all derived from one original cell. Such a population is called a clone, hence the term monoclonal.

An intermediate state between MGUS and myeloma, which may represent a form of pre-myeloma rather than a subtype of myeloma, is known as smouldering myeloma. In this condition a paraprotein is present but the patient is free of symptoms. The survival of patients with MGUS or smouldering myeloma is considerably longer than for true myeloma.

When a myeloma-like condition is confined to a single location, which may be in the bone or in soft tissues, it is referred to as solitary plasmacytoma. An uncommon complication of myeloma is amyloidosis in which there is deposition of an abnormal protein (amyloid) in various tissues.

There are several different types of antibody molecules with different functions within the body. These are called IgM, IgG, IgA, IgD and IgE (Ig is the abbreviation for immunoglobulin, another term for antibody molecule). In about three-quarters of all cases of myeloma the paraprotein present will correspond to one type of antibody molecule. The disease may therefore be referred to as IgG, IgA, IgD or IgE myeloma. IgM myeloma is very rarely seen. Cases where IgM is the dominant type are usually classified as Waldenstrom's macroglobulinaemia<sup>2</sup>. In the remaining cases there is either no detectable paraprotein, or there is a mixed Ig type protein, or the paraprotein cannot be classified as matching any of the Ig types.

Each type of myeloma may show slightly different patterns of disease. For example patients with IgD myeloma more frequently develop an associated condition called plasma cell leukaemia<sup>3</sup> and have kidney damage. If patients wish to know more about which subtype they have they should discuss this with their specialist.



<sup>2</sup> There is a separate publication on Waldenstrom's macroglobulinaemia available from Leukaemia Research.

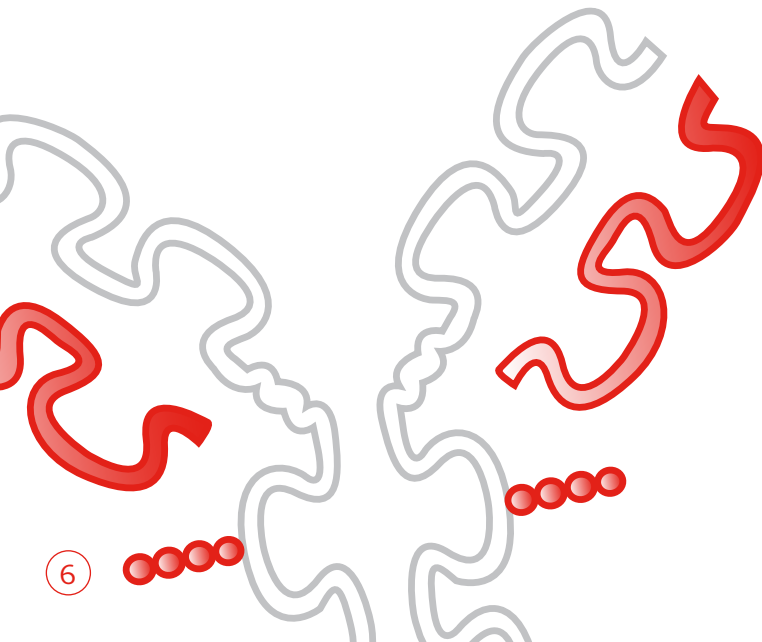
<sup>3</sup> There is a separate publication on plasma cell leukaemia available from Leukaemia Research.

## What causes multiple myeloma?

**There are no clearly defined risk factors for multiple myeloma. Among those that have been suggested are exposure to high levels of ionizing radiation and certain occupational and chemical exposures.**

The incidence of the disease was initially reported to be increased among survivors of the Hiroshima and Nagasaki atomic bomb explosions. Long-term follow-up however has shown no evidence of any excess of cases among survivors.

Myeloma is not an inherited condition and there is no clear evidence of an excess of cases among the close relatives of patients with myeloma or other cancers. There have, however, been reports of families with several cases. The significance of this remains unclear.



# What are the signs and symptoms of multiple myeloma?

**At the time of diagnosis about 70% of patients have pain of varying intensity associated with the presence of areas of bone destruction called lytic bone lesions. Many patients with bone lesions suffer broken bones (pathological fractures). These are breaks which may occur as a consequence of minimal trauma. The most common sites of pain are the lower back and the ribs. As back pain is very common in the general population this may lead to a delayed diagnosis.**

Patients with myeloma may show:

- Bone related symptoms
  - ✦ persistent unexplained backache, associated with loss of height and osteoporosis (bone thinning), especially in males and pre-menopausal women
  - ✦ symptoms suggestive of spinal cord/nerve root compression including weakness in the lower limbs and bladder problems
- Bone marrow related signs and symptoms
  - ✦ frequent, persistent infections, in particular pneumonia and chest infections are very common in myeloma because in about three-quarters of all patients production of normal antibodies is suppressed
  - ✦ anaemia; if patients are anaemic they may tire easily and may become breathless even after mild exertion. This is because there is a reduction in the number of red blood cells although the red cells appear normal under the microscope
  - ✦ low white cell count and/or platelet count

○ Abnormal laboratory results

- ❖ poor kidney function
- ❖ hypercalcaemia, i.e. high levels of calcium in the blood
- ❖ persistent high ESR (erythrocyte sedimentation rate) or plasma viscosity. ESR is a test which is affected by levels of protein in the blood and is usually very much higher than normal in myeloma
- ❖ A raised abnormal protein in the blood called a paraprotein; when this is found in the urine it is called Bence Jones protein
- ❖ If the levels of plasma protein are high the blood becomes thick (hyperviscosity) and this can reduce blood flow. Patients should seek prompt medical advice if they experience any of these signs including excessive weariness, confusion, headaches, temporary disturbances of vision and any abnormal bleeding (e.g. bleeding gums when brushing teeth).



# How is multiple myeloma diagnosed?

**Clinical presentation of myeloma can vary widely. There are no definite signs or symptoms which are seen only in this disease. Some patients are free of symptoms at the time of diagnosis with the disease being detected as a result of routine blood tests.**

On the other hand some patients may have areas of tenderness over a site of bony involvement, abnormal curvature of the spine or pathological fractures. These clinical signs are suggestive of myeloma but not unique to this disease. If the spinal column is involved then various neurological abnormalities may be detected including weakness and loss of sensation in the lower limbs together with bladder problems.

The diagnosis of myeloma depends on three abnormal findings:

- 1 ✦ Bone marrow containing more than 10% plasma cells (normally no more than 4% of the cells in the bone marrow are plasma cells)
- 2 ✦ X-rays showing punched out lesions of the bones or generalized thinning of the bones
- 3 ✦ Blood serum and/or urine showing the presence of an abnormal protein

## Bone marrow sampling

The demonstration of excessive numbers of plasma cells in the bone marrow is part of the definition of multiple myeloma. The plasma cells may also appear different to those seen in normal bone marrow. Bone marrow involvement may be patchy but it is usual to detect the presence of myeloma cells in a sample of marrow collected from a single site. If bone marrow involvement is extensive then plasma cells may even be present in the blood, though this is uncommon (about 15% of cases).

## Skeletal features

About 70% of patients with myeloma will have readily detectable, distinctive 'punched out' bone lesions which can be seen on an X-ray survey of the bones. These are areas where there has been extensive bone destruction caused by myeloma cells. In about 20% of cases there is widespread loss of bone density without distinct myeloma-type lesions. The damage is similar to that seen in osteoporosis in post-menopausal women.

In 10% of patients with a diagnosis of myeloma the skeletal survey does not reveal bone damage. MRI (magnetic resonance imaging) scans may be useful for detecting local areas of damage especially within the bones of the spinal column. MRI is similar to an X-ray but does not use radiation. It shows soft (non-bony) tissues much more clearly than X-rays. An alternative test, which is less sensitive than MRI, is called a CAT or CT scan. This uses X-rays but shows more detail than a standard X-ray.

## Paraproteins

Antibodies are made by B cells and consist of two types of protein molecules, called heavy chains and light chains. Two heavy chains and two light chains join together to form an antibody molecule. In the great majority of cases of myeloma both heavy and light chains are produced in excess. In a minority of cases there may be overproduction of only light chain or, very rarely, only heavy chain proteins. In about 60% of cases an abnormal protein may also be found in the urine. This is made up of an excess of light chains and is called Bence-Jones protein.

High quantities of free light chains can cause kidney damage which may be very severe. In about 25% of patients, kidney failure can occur and this may become a serious clinical problem.

Measuring the amount of paraprotein in the blood or urine is of value in the diagnosis of myeloma and in monitoring the response to treatment.

The standard tests used are called protein electrophoresis and immunofixation. A relatively new test has been introduced which detects fragments of paraprotein called free light chains. This blood test, called the 'serum free light chain assay', may be particularly valuable in diagnosis of patients who have no monoclonal protein in serum or urine, this is light chain myeloma or non-secretory myeloma. If this test is being used, the specialist will explain the significance of any abnormal results. Recent studies have indicated that results of this assay may be of particular value in predicting when MGUS or smouldering myeloma are likely to progress to true myeloma.

## Serum $\beta_2$ - microglobulin ( $S\beta_2$ - M)

All nucleated cells in the body have a surface marker called  $\beta_2$ - microglobulin<sup>4</sup>. Free  $\beta_2$ - M is present in the blood, this is called serum  $\beta_2$ - microglobulin ( $S\beta_2$ - M). Normally  $S\beta_2$ - M is only present in very small amounts. In myeloma the amount of  $S\beta_2$ - M is increased; the extent of which gives a useful measure of how advanced the disease is in a given patient.

## Serum albumin

Serum albumin is the most common protein in the blood. It binds to, and transports, fats and other compounds within the bloodstream. For reasons that are not well understood the amount of albumin in the serum is reduced in patients with myeloma, and the more severe the illness, the lower the serum albumin level. For this reason serum albumin is checked frequently in all patients with myeloma.

## Other investigations

A number of other investigations may be of value in confirming the diagnosis, in assessing the likely prognosis and in monitoring the response to treatment. All patients with a confirmed diagnosis of myeloma will require regular monitoring of kidney function. A number of specific blood tests may be carried out including measurement of calcium and uric acid.

<sup>4</sup>  $\beta_2$ - M allows cells to interact with the immune system.

In most forms of leukaemia and related diseases the study of changes in the genetic structure of chromosomes has been found to be of value in predicting the response to treatment and the likely outcome. This is known as cytogenetics. Abnormal cytogenetic results are seen in about 70% of patients with myeloma. The clinical significance of these abnormalities is not yet known but is under investigation.



## How is multiple myeloma staged?

**In most cancers, some form of staging is used to assist in treatment planning and in assessing likely prognosis. Staging in solid cancers relates chiefly to the spread of the tumour from its original site, this is called metastasis. Staging based on spread is not helpful for myeloma because it is, by definition, widely spread in the bone marrow at the time of diagnosis.**

Until recently, the most commonly used staging system for myeloma was the Durie/Salmon system. This system was based on estimating the number of myeloma cells (i.e. the tumour burden) and on specific properties of the cells, such as the rate of cell division. This was of very limited value in predicting the likely prognosis for individual patients and has now been replaced by the International Staging System (ISS). The ISS is based on the results of two key laboratory tests called serum  $\beta_2$ -microglobulin ( $S\beta_2$ -M) and serum albumin.

Stage	Criteria	Median survival
I	$S\beta_2$ -M <3.5mg/l and albumin $\geq$ 3.5g/dl	62 months
IIA	$S\beta_2$ -M <3.5mg/l and albumin <3.5g/dl	44 months
IIB	$S\beta_2$ -M <3.5 to <5.5mg/l	
III	$S\beta_2$ -M $\geq$ 5.5mg/l	29 months

### [Median Survival a note

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 realize that not all deaths of patients with myeloma are related to their illness. 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.]

# How is multiple myeloma treated?

## Principles of treatment<sup>5</sup>

**Some patients are diagnosed by chance at a time when they are free of symptoms. These are called asymptomatic patients. Such patients are not normally treated unless there is evidence from laboratory tests, X-rays or scans that the disease is progressing. Studies have shown that there are no benefits from early treatment of these patients. Asymptomatic patients typically have measurements of blood serum and urine paraprotein levels at three-monthly intervals. X-ray and bone marrow examinations will be done routinely at less frequent intervals or when new signs or symptoms are seen. This is often referred to as ‘watch-and-wait’. When X-rays show evidence of bone disease patients should commence treatment immediately.**

Treatment of myeloma can be divided into (a) supportive measures which are aimed at controlling the effects of the disease on other tissues and organs, and (b) treatment of the underlying disease which is known as definitive treatment. Supportive care of the patient includes measures to prevent problems such as kidney damage and infection. Definitive treatment of the disease may be with conventional chemotherapy or with high-dose chemotherapy in association with stem cell transplantation.<sup>6</sup>

Supportive treatment is aimed at achieving the best possible quality of life. Definitive treatment aims to eliminate all detectable signs of the disease, both clinically and by laboratory tests. This is called a complete response. Many patients will experience a marked improvement in their condition which falls short of a complete response. This is known as a partial response.

<sup>5</sup> The treatment sections of this booklet are based on guidelines developed by the UK Myeloma Forum on behalf of the British Committee for Standards in Haematology. The UK Myeloma Forum has a website at [www.ukmf.org](http://www.ukmf.org)

<sup>6</sup> There is a separate publication on bone marrow and stem cell transplantation available from Leukaemia Research.

When a patient's condition does not improve at all the patient is said to have refractory or resistant disease. A return of disease in plateau phase is known as relapse or progression.

Definitive treatment for myeloma may also affect production of normal blood cells by the bone marrow. This affects neutrophils, red blood cells and platelets. Neutrophils are one type of white blood cell which play a very important part in the body's defences against bacterial and fungal infections. If red cell production is affected, patients will become anaemic. Platelets are part of the clotting system and very low levels may place patients at risk of bleeding and/or bruising.

## Supportive measures

Good supportive care<sup>7</sup> is crucial to maintaining quality of life in patients with myeloma regardless of the definitive treatment they are receiving.

## Kidney function

There are several causes of kidney damage in patients with myeloma. Abnormal paraproteins may be deposited in the kidney where they can block tubules. Dehydration and high blood calcium or urea levels can also contribute to kidney damage as can severe infections. All patients with myeloma must maintain a high fluid intake to prevent dehydration. This intake should be at least three litres (5-6 pints) a day, more in hot weather. If the disease affects kidney function, patients may need dialysis (an artificial kidney). Patients who do need this will receive information on the procedure from their specialist or from the kidney unit where they are being treated.

Some drugs may damage the kidney, for example non-steroidal anti-inflammatory drugs (NSAID) such as aspirin and ibuprofen and also some antibiotics. If a patient or carer is buying over-the-counter pain relief they must check with the pharmacist that these do not contain NSAIDs.

<sup>7</sup> There is a separate publication on supportive care available from Leukaemia Research.

Paracetamol and codeine based pain killers may be suitable but all patients must check with their specialist what, if any pain killer, they recommend. Many flu and cold remedies contain aspirin so caution is again necessary.

It may be advisable to obtain a small MedicAlert bracelet<sup>8</sup> (also available as a necklace) which, in an emergency, will alert medical teams to the patient's special requirements. It also carries a phone number which health professionals can ring to check on other relevant medical history.

## Hypercalcaemia

High levels of calcium in the blood are seen in about a quarter of myeloma patients. This is chiefly a consequence of the increased bone destruction releasing calcium into the bloodstream. Raised calcium levels may cause nausea, vomiting and polyuria (frequent passing of excessive amounts of urine), constipation and a dry mouth. If the calcium level is very high there may be a need for a rapid reduction using intravenous fluids, corticosteroid drugs and drugs called bisphosphonates. Bisphosphonates are also used in routine treatment of myeloma and are described in more detail later in the booklet.

## Bone disease and pain management

A wide range of analgesic drugs is suitable for the control of pain in patients with myeloma. Caution is required in the use of non-prescribed drugs by myeloma patients. This is described in the section on kidney function. A relatively new class of drugs called bisphosphonates has been shown to help control bone disease in myeloma. As soon as patients require active treatment they should begin long-term treatment with bisphosphonates.

Orthopaedic surgery may be required to prevent or to repair pathological fractures in the long bones of the arms or legs. Radiotherapy may be given to treat severe local pain. If surgery is required then radiotherapy will be delayed to allow the surgical wounds to heal fully. In order to minimise bone damage,

<sup>8</sup> MedicAlert Foundation, 1 Bridge Wharf, 156 Caledonian Road, London N1 9UU, Telephone: 0800 581 420 or 020 7833 3034, e-mail address: [info@medicalert.co.uk](mailto:info@medicalert.co.uk)

patients should endeavour to remain mobile. Physiotherapy and the use of aids such as spine supports may assist with this.

## Hyperviscosity

Hyperviscosity is a condition which occurs when the fluid portion of the blood (plasma) contains high amounts of paraprotein. This thickens the blood and reduces its mobility which may lead to circulatory problems. If there are signs or symptoms of hyperviscosity such as shortness of breath, confusion, headaches and visual disturbances, the specialist may recommend urgent treatment to lower the paraprotein levels. Treatment may include plasma exchange, which is a procedure involving the separation and removal of the plasma from the blood and the return of red blood cells, white blood cells and platelets to the patient, along with replacement fluid or new plasma. If patients with hyperviscosity require transfusions of red blood cells, this may cause further thickening of the blood leading to a stroke. To avoid this a volume of blood is removed equal to the volume of the transfusion. For example, if a patient receives a litre of packed red cells they have a litre of blood removed. This is known as an exchange transfusion. When paraprotein levels are very high, prompt chemotherapy with rapidly acting drugs or combinations of drugs is of value.

## Spinal cord compression

Spinal cord compression is a serious complication which may arise in patients who have myeloma. Rarely, it may be present at the time of diagnosis but more frequently it develops during the course of the illness. Spinal cord compression is an emergency and patients with the following signs or symptoms should contact their doctor or the hospital urgently:

- Pain in the back or radiating from the back (pain can be exacerbated by coughing or movement)
- Loss of sensation in the lower part of the body
- Inability to pass urine
- Bowel and bladder dysfunction; incontinence

Any patient who is thought to have spinal cord compression will be admitted to hospital immediately. An MRI scan will allow doctors to determine the site and extent of the myeloma mass. If MRI scanning is not available, or is not suitable for a given patient, then CAT scans may be used although these are less informative. It is normal to immediately commence treatment with dexamethasone in order to minimise the risk of irreversible damage to nervous tissue. The treatment of choice for spinal cord compression is local radiotherapy followed by chemotherapy. Surgery is generally indicated only if there is spinal instability as a result of bone loss.

## Infections

Infection is a serious and potentially life-threatening complication of myeloma, especially when patients are receiving chemotherapy. All patients should have 24-hour access to advice either directly from their specialist or through their primary care team. Infections of the upper respiratory tract (the nose and throat) are relatively easy to treat but can give rise to pneumonia. It is very important that myeloma patients seek prompt medical advice if they develop any type of infection. If patients develop severe generalized infections they will need to be admitted to hospital to receive intravenous antibiotic therapy.

Annual 'flu vaccination should be given by the GP surgery and patients will usually be contacted and asked to arrange an appointment. Times when 'flu vaccination is recommended are normally publicised on TV and in the newspapers. Patients should contact their doctor if they are not called in to receive vaccination.

## Anaemia

Over two-thirds of myeloma patients have anaemia at the time of diagnosis. The anaemia is not usually severe unless there are other contributing factors such as blood loss or dietary deficiencies. Mild anaemia does not usually require treatment. If the anaemia is severe enough to limit the patient's daily

activities then blood transfusions may be given. There is a need for particular caution in transfusing patients who have signs or symptoms of hyperviscosity (see above).

Anaemia usually improves on effective treatment of the underlying myeloma. It may re-occur at the time of relapse or progression of the disease or as a feature of late-stage disease. If anaemia does not resolve in a patient who is responding to chemotherapy, it may be a consequence of poor kidney function. The kidneys make a substance called erythropoietin (EPO), which stimulates the bone marrow to make red blood cells. For this reason, erythropoietin injections may improve the situation in this group. Occasionally patients with normal kidney function have persistent anaemia and erythropoietin may also be of value for these patients.

## Bisphosphonates

Among the main causes of disability and death in myeloma are bone pain, hypercalcaemia and pathological fractures. These are caused by the interaction between myeloma cells and cells called osteoclasts and osteoblasts which are continually remodelling bone. In myeloma the balance between osteoclast and osteoblast activity is disturbed and this leads to the destruction of bone tissue. A class of drugs called bisphosphonates can bind to the surface of bones and markedly reduce skeletal damage and thus the need for surgery and radiotherapy.

Clinical studies have clearly shown that the maximum benefit is achieved when bisphosphonates are given before there is evidence of bone damage. The main bisphosphonates currently used in myeloma therapy are clodronate (which is given daily by mouth) and pamidronate or zoledronate (each of which is given by monthly infusions into a vein).<sup>9</sup> All forms of bisphosphonates must be used with care in patients with renal disease .

<sup>9</sup> A bisphosphonate called etidronate has been found useful in other conditions but is not effective for myeloma and may even worsen bone damage.

## Radiotherapy

Radiotherapy may be of value in controlling symptoms in patients who have refractory or resistant disease, i.e. disease which is not responding to either established treatments or to the newer agents. It may also be used to control symptoms, particularly bone pain, for patients whose disease is responding to treatment. It is important that patients should understand that discussions about symptomatic (palliative) care do not mean that their treatment has failed or implies that their condition is terminal. On the contrary, it should be seen as another treatment option.


## Psychological problems

Patients with myeloma may be depressed or anxious. Such problems should be actively managed with support from a psychiatric or clinical psychology team.

## Treatment of primary disease

Many patients with myeloma will be invited to take part in a research study (i.e. clinical trial<sup>10</sup>) to compare two or more different treatments. These studies are vital in order to develop better treatments. Previous studies in myeloma have led to major advances in treatment. Not all patients are eligible to take part in such studies; this is particularly true when patients have other illnesses such as heart disease or diabetes, which might make it difficult to interpret the results. Patients will be given full details of the study, the questions it is designed to answer, the alternative treatments being offered and standard treatments available outside the study. It is important to stress that entry into such studies is entirely voluntary.

There are two major options for the definitive treatment of myeloma:

- 1  Chemotherapy aimed at achieving a stable response (plateau) but without any attempt to eradicate the disease. This may be achieved with:
  - Single drugs — usually melphalan or cyclophosphamide, each of which may be given with or without prednisolone

<sup>10</sup> A booklet on clinical trials is available from Leukaemia Research.

- Combination chemotherapy with relatively mild drugs
- 2 ∴ Alternatively, in younger and/or fitter patients it may be planned from the outset to give more intensive chemotherapy, normally followed by a bone marrow or stem cell transplant. In myeloma the majority of transplants are carried out using the patient's own stem cells. This is termed an autologous transplant. If this is being considered it is important to avoid the use of chemotherapy drugs which may damage stem cells. Patients who are to receive a transplant typically receive initial treatment with:
  - Combination therapy of a type unlikely to damage stem cells

This is usually followed by high-dose chemotherapy and a stem cell transplant.

## **Option 1: Chemotherapy**

### **∴ Melphalan (with or without prednisolone)**

This is usually given by mouth over four to seven days at approximately monthly intervals for six to twelve months. About half of all myeloma patients will show an improvement in their condition (a response). Complete responses are rare. Usually the effect of the drug is gradual and it may take months to achieve the best results. Most patients whose condition responds to melphalan will achieve a stable state (plateau) lasting for about 18 months to two years. Plateau phase is characterised mainly by a stable paraprotein level but also a stable blood count and clinical features. The duration of plateau phase does not appear to be increased by continuing chemotherapy so most patients will stop drug treatment once they have achieved this phase.

Some centres use melphalan alone and others use it in combination with prednisolone (this is often abbreviated MP or M&P therapy). Prednisolone is taken orally (as a tablet). This drug should be avoided if an autologous stem cell transplant is planned because it damages stem cells. Melphalan, with or without prednisolone is usually well tolerated. There may be mild nausea but hair loss is rare. Bone marrow function may be affected, leading to a drop in blood counts.

## ∴ **Cyclophosphamide (with or without prednisolone)**

Cyclophosphamide is used in a similar way to melphalan with similar benefits but is less toxic to the bone marrow. It can be used in patients whose neutrophil or platelet counts are too low for melphalan to be given. It can be given orally or intravenously on a weekly schedule. The side effects are similar to those seen for melphalan alone or with prednisolone.

## ∴ **Alkylating agent based combination chemotherapy regimens**

Melphalan and cyclophosphamide both belong to a group of drugs called alkylating agents. A number of combinations have been devised which include melphalan and cyclophosphamide plus two or more of the following drugs: vincristine, adriamycin, prednisolone and carmustine (BCNU). The combination treatment with Adriamycin™, BCNU, cyclophosphamide and melphalan is called ABCM. Combination therapy is more complicated than single drug treatment as it usually requires intravenous therapy but may give slightly better outcomes.

## ∴ **VAD and related regimens**

When a patient is being considered for treatment with an autologous stem cell transplant it is very important to select drug combinations which are not likely to harm the stem cells. One of the most widely used combinations is called VAD which stands for vincristine, doxorubicin (Adriamycin™) and high-dose dexamethasone (a steroid). This is given as a four day continuous infusion. A high proportion of patients will respond to VAD and 10-25% achieve complete remission. VAD is very suitable for patients with hyperviscosity for whom a rapid response is needed to prevent organ damage. There are a number of other, similar regimens which some doctors prefer to use instead of VAD.

As well as being the treatment of choice for patients who are to undergo autologous stem cell transplants it is also suitable for patients with kidney

damage as the drugs are not harmful to the kidney and no dose reduction is required. The primary disadvantages are the need to put a central venous line<sup>11</sup> in place and the high incidence of steroid-related side-effects (these include an increased risk of infection, rise in blood pressure, peptic ulcers, diabetes mellitus, osteoporosis).

VAMP and C-VAMP are modifications of the VAD regimen in which high-dose dexamethasone is replaced by intravenous methylprednisolone in an attempt to reduce the level of steroid-related toxicity. C-VAMP also includes weekly intravenous cyclophosphamide.

Oral idarubicin and dexamethasone regimens have been developed in an attempt to avoid intravenous drug administration. Idarubicin is given by mouth for four days per cycle along with high-dose dexamethasone (HDD). There are no data on long-term outcomes for this combination but stem cell harvesting does not appear to be compromised. The addition of cyclophosphamide to this regimen makes it very similar to the widely used C-VAMP regimen.

## ⚡ **Thalidomide**

Thalidomide is a drug which was used briefly in the 1950/60s for prevention of morning sickness during pregnancy. It was withdrawn from the market because it was found to cause severe congenital abnormality of limb development. It was re-introduced, under stringent controls, for treatment of some forms of leprosy and severe auto-immune diseases. More recently it has been used for treatment of certain blood cancers. Because of concern about the potential risks and because of the side effects of the drug a number of thalidomide-derived drugs are now being tested. It is hoped that these drugs, which are known as immunomodulatory drugs or iMiDs for short, will be more effective and much safer.

<sup>11</sup> A central venous line is a catheter which is surgically inserted through the chest wall into a large vessel to facilitate intravenous administration of drugs.

Thalidomide both prevents formation of new blood vessels and modifies the behaviour of the immune system. It has shown promise against myeloma in preliminary trials and is now established as a second-line therapy, that is, it is used for patients whose disease did not respond to or became resistant to first-line drug(s).

One aim of the current UK Myeloma IX study is to compare use of thalidomide in combination with cyclophosphamide and dexamethasone (CTD) against MP (melphalan and prednisolone) for patients who are not being considered for a transplant. Patients entering the study will also be randomly allocated to receive either clodronate or zoledronate as bisphosphonate therapy.

## **Option 2: Transplant based therapy**

### **∴ High-dose therapy followed by autologous stem cell transplantation<sup>12</sup>**

This usually comprises standard chemotherapy followed by high doses of melphalan alone or in combination with total body irradiation. This gives very effective treatment against the myeloma but will destroy the patient's bone marrow. For this reason high-dose therapy must be followed by a stem cell transplant (SCT) to repopulate the bone marrow and restore blood cell production. For patients who are intended to receive a stem cell transplant, the Myeloma IX study is comparing the effectiveness of CVAD (cyclophosphamide, vincristine, Adriamycin™ and dexamethasone) and CTD (cyclophosphamide, thalidomide and dexamethasone) as the chemotherapy options prior to high dose therapy and the transplant.

Usually an autologous transplant is carried out whereby the patient's own stem cells, which have been harvested and stored prior to high-dose therapy (HDT) are used. Studies have confirmed that this treatment extends survival significantly and it is now the accepted standard of care for younger, fitter patients. Although this approach extends survival over 90% of all patients will relapse and the procedure is not considered curative. Attempts have

<sup>12</sup> This is often abbreviated as HDT/ASCT.

been made to reduce the relapse rate by sorting and selecting bone marrow cells in the laboratory in order to reduce the number of myeloma cells and concentrate the normal stem cells. There is currently no evidence to show that this reduces the risk of relapse. Some centres have carried out procedures in which two or more autologous transplants are carried out one after the other. These are known as tandem or double transplants. Again there is no clear evidence that this improves outcomes.

## ∴ **Allogeneic stem cell transplants**

The role of allogeneic (donor) transplantation using a tissue-matched sibling as a donor in the treatment of myeloma is controversial, chiefly because both transplant related mortality and relapse rate are high. It does, however, offer a chance of a complete cure. Patients who are transplanted in first remission have an estimated 60% chance of entering complete remission and one-third of these patients remain free of disease with a very low risk of relapse. For younger patients, particularly females, the potential benefits may outweigh the risks of the procedure. Patients who have relapsed after this type of transplant may benefit from a procedure called donor lymphocyte infusion.<sup>13</sup>

Transplants from donors other than siblings have a particularly high mortality rate and are not currently recommended. Transplants employing reduced conditioning (mini-transplants or non-myeloablative transplants) use less intensive treatment prior to the transplant which is not intended to completely destroy the host's marrow but merely to suppress the immune system sufficiently to prevent graft rejection. The less toxic conditioning means that this type of transplant may be feasible for patients who are too old or too ill to safely undergo a conventional transplant. The safety, effectiveness and outcomes of reduced intensity conditioning donor transplantation are being studied in the Myeloma IX trial.

<sup>13</sup> Donor lymphocyte infusion involves injection of cells from the immune system of the stem cell donor. It seeks to eliminate myeloma cells by an immune mechanism.

## ∴ Interferons

Interferons are a family of proteins produced by white blood cells which inhibit the division and growth of cancer and virus-infected cells. The major role for interferons in the treatment of myeloma appears to be as maintenance therapy given during the plateau phase. In this context they prolong plateau phase and overall survival; in a high proportion of patients, however, side effects of interferon are severe and may be unacceptable. There is no evidence that the use of interferon, alone or in combination is beneficial as an initial treatment for myeloma.

## Treatment of refractory or relapsed disease

### ∴ Refractory disease

There is a lack of evidence from clinical trials on the ideal management of refractory disease. Patients who did not respond when treated with melphalan may benefit from VAD or a VAD-like regimen and vice versa. A high proportion of patients in this group will not respond to any standard chemotherapy agent and, until recently, options for treatment were very limited.

Myeloma, which is refractory to standard therapy, may respond well to thalidomide, either used alone or with steroids. Thalidomide alone has been shown to produce a response in 30% of patients with refractory or relapsed myeloma. Many patients, however, find the side-effects of thalidomide unacceptable and similar drugs are being developed in order to minimise these.

The new generation of thalidomide derived drugs, called iMiDs (immunomodulatory drugs or thalidomide analogues) is being studied initially in the context of refractory or relapsed disease.

A newer drug called bortezomib (Velcade™) is being studied for its effectiveness in this situation. Velcade blocks a biochemical pathway which is very important to myeloma cells but much less important in normal cells. This leads to death of a high proportion of the tumour cells, without the severe side effects seen with many other cell killing drugs.

## ⌚ Relapsed disease

If patients relapse early in the course of their treatment the choice of further chemotherapy is difficult and quality of life and symptom relief become the primary aims of treatment. Patients who relapse after a long plateau stage often respond to further conventional treatment.

Current options for treatment of relapse include the same chemotherapy that was used for initial treatment, i.e. melphalan or cyclophosphamide, each of which may be given with or without prednisolone; combination regimens, including VAD regimens and oral idarubicin with high-dose dexamethasone, or high-dose therapy followed by an autologous stem cell transplant. Thalidomide is gaining a place in treating patients with relapsed disease which is refractory to other therapy. Steroids alone may be useful in second or subsequent relapse or in patients in whom chemotherapy is not feasible.

Bortezomib, and the iMiDs are being used in clinical studies to determine their potential benefits for treatment of relapse of disease.

## ⌚ Monoclonal antibodies

Monoclonal antibodies target specific markers on the surface of the myeloma cell and offer a way to attack the myeloma cells with minimal or no impact on surrounding tissues. They are currently being studied for their potential use in treating refractory or relapsed myeloma.

## ⌚ Treatment of patients with kidney failure

About half of all patients will have renal impairment at some stage. Up to 20% of patients have renal failure at the time of diagnosis. Five to ten percent of patients will have advanced renal failure requiring dialysis or other supportive treatment. Early intervention at the first indications of kidney impairment is necessary to prevent long-term renal damage.

Key points in the early treatment of patients with renal failure are:

- Rehydration with intravenous fluid
- Avoid drugs which are toxic to the kidneys
- Rapid and vigorous treatment of infection
- Correction of high calcium levels in the blood – if necessary with intravenous bisphosphonates. Bisphosphonates must, however, be used with caution in this situation
- A tissue biopsy may identify the cause(s) of kidney disease and guide treatment but is not essential

The choice of chemotherapy is important as both melphalan and cyclophosphamide are excreted via the kidneys and may require dose reduction in the presence of renal damage.

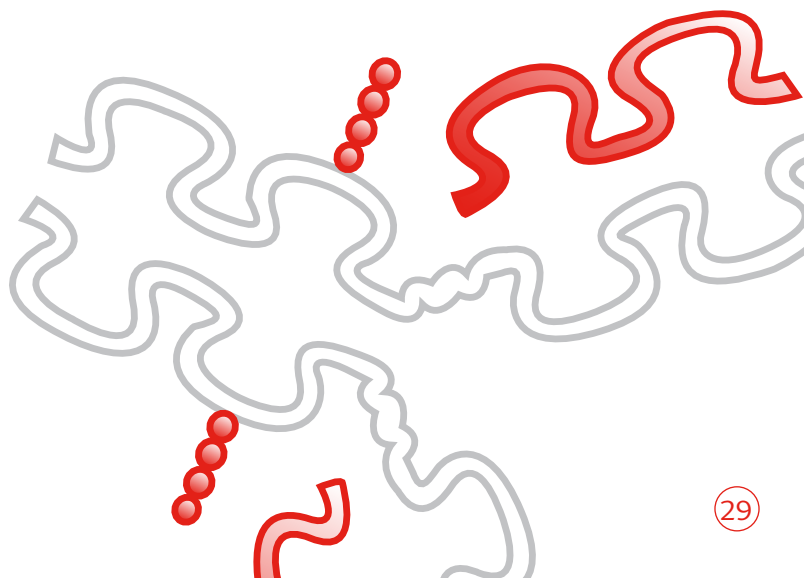
VAD-based regimens and high-dose dexamethasone are recommended for initial therapy because they are less toxic to the kidneys. High-dose dexamethasone can be given as immediate therapy with a prompt response.

In later stages dialysis may be necessary, either using an artificial kidney or by a method called peritoneal dialysis. If this is necessary patients will be given full details by the dialysis team. Only a very small selected group of patients can be considered for renal transplantation. High-dose therapy followed by an autologous stem cell transplant can be offered to patients with renal disease but it should only be done in a centre with appropriate experience.



## Follow-up

Follow-up is important for the minority of patients diagnosed with early-stage disease, who are free of symptoms. There is wide variation in the length of time for which the disease remains stable in this group. It is important that patients are followed-up in order to permit early treatment of progressive disease which may minimise bone and kidney damage. Patients in plateau phase are followed up to detect evidence of relapse so that treatment may be initiated.



## Prognosis

**There is significant variation in survival after the diagnosis of myeloma. With current treatments more than 50% of all patients are alive and well at three to four years after their disease is diagnosed. The only person who can advise a patient on their likely prognosis is their own specialist. There is currently no evidence that any treatment is capable of curing myeloma although it is clear that some therapies can significantly prolong survival.**



## Summary

**Multiple myeloma is a form of cancer affecting a specific type of lymphocyte called the plasma cell. Plasma cells are normally responsible for the production of antibodies.**

The condition is called multiple myeloma because most patients have evidence of disease at a number of different bony sites in the body. The disease is accompanied by a breakdown in the structure of the bones. This is due to an increased activity of cells in the marrow which continually break down and reform bone. In myeloma the destruction exceeds replacement and 'holes' in the bones result. This leads to the release of large amounts of calcium into the blood which may lead to kidney damage.

In normal circumstances, the antibody molecules present in the blood are varied in their structure, reflecting the large number of infections they may be required to combat. In patients with myeloma very large quantities of a single type of antibody are produced. This is called a paraprotein and it is present in the blood and/or urine in about 99% of cases. Recurrent severe infections can occur in myeloma patients that may be life-threatening because there is a marked reduction in the level of antibodies (gamma globulins) in the blood.

In about 90% of cases there is measurable damage to bone. In most instances this is in the form of local areas of bone loss called lytic lesions. There can be an increased level of calcium in the blood. There is a very high incidence of kidney disease in myeloma which is caused principally by the deposition of large amounts of paraprotein.

The cornerstone of treatment for myeloma is good supportive care. Radiotherapy and surgery may be of value in dealing with specific problems or where patients cannot receive chemotherapy. A key development in improving the quality of life of myeloma patients has been the introduction

of drugs called bisphosphonates. These markedly reduce the bone destruction associated with myeloma which is one of the most distressing features of the disease. There is preliminary evidence to suggest that some bisphosphonates may also kill myeloma cells.

Treatment with anti-cancer drugs (chemotherapy) can significantly prolong survival but the myeloma cells are never fully eliminated by drugs used at conventional doses. Stem cell transplants may be considered for younger fitter patients, generally under the age of 65 years. It may be either autologous (using the patient's own stem cells) or allogeneic (using a tissue-matched brother or sister as donor).

A recent innovation in the treatment of myeloma is the use of thalidomide. This drug acts to prevent formation of new blood vessels and has shown promise against myeloma in clinical trials. However many patients find the side-effects of thalidomide unacceptable and similar drugs are being developed which carry less severe side-effects. A recently introduced drug called bortezomib (Velcade™) has shown promise in the treatment of refractory or relapsed disease.



## Typical normal values for blood test results

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

The following patient information booklets are available free of charge from Leukaemia Research. You can download them from our website or request copies by phone or post (see form inside):

Leukaemia and Related Diseases

Acute Promyelocytic Leukaemia (APL)

Adult Acute Lymphoblastic Leukaemia (ALL)

Adult Acute Myeloid Leukaemia (AML)

Aplastic Anaemia (AA)

Bone Marrow and Stem Cell Transplantation (BMT)

Childhood Acute Lymphoblastic Leukaemia (ALL)

Childhood Acute Myeloid Leukaemia (AML)

Chronic Lymphocytic Leukaemia (CLL)

Chronic Myeloid Leukaemia (CML)

Hodgkin's Lymphoma (HL)

Multiple Myeloma (MM)

Non-Hodgkin's Lymphoma (NHL)

The Myelodysplastic Syndromes (MDS)

The Myeloproliferative Disorders (MPD)

Clinical Trials

Chemotherapy – what do I need to know?

Donating stem cells – what's involved?

Donor Lymphocyte Infusion (DLI) – what's involved

Supportive care

The Seven Steps – Blood & Bone Marrow Transplantation

Young Adults with a blood cancer – what do I need to know?

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