



Myeloma
Patients
Europe



MULTIPLE MYELOMA

A Patients' Guide

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1. Introduction

Although myeloma is the second most common form of blood cancer, it only represents 1% of cancers¹. Many people have never heard of myeloma, so being given a diagnosis of myeloma can be quite frightening. In some ways it can be more worrying than being told you have another type of cancer, if you have not heard the name before.

You will have a lot of questions, and you will learn a lot about myeloma in the weeks and months to come. It will take time for it to begin to make sense.

This guide gives the answers to most of the things you want to know about myeloma: how it may affect you, what treatments you may have, and how much or how little will change in what you are able to do.

Learning about it will help you to cope with all the feelings that have come with the diagnosis. It may be a good idea not to read it all at once, but to come back to it at any time when you want to know about a particular aspect, or to refresh your memory.

¹ International Agency for Research on Cancer: GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012. http://globocan.iarc.fr/Pages/fact_sheets_population.aspx

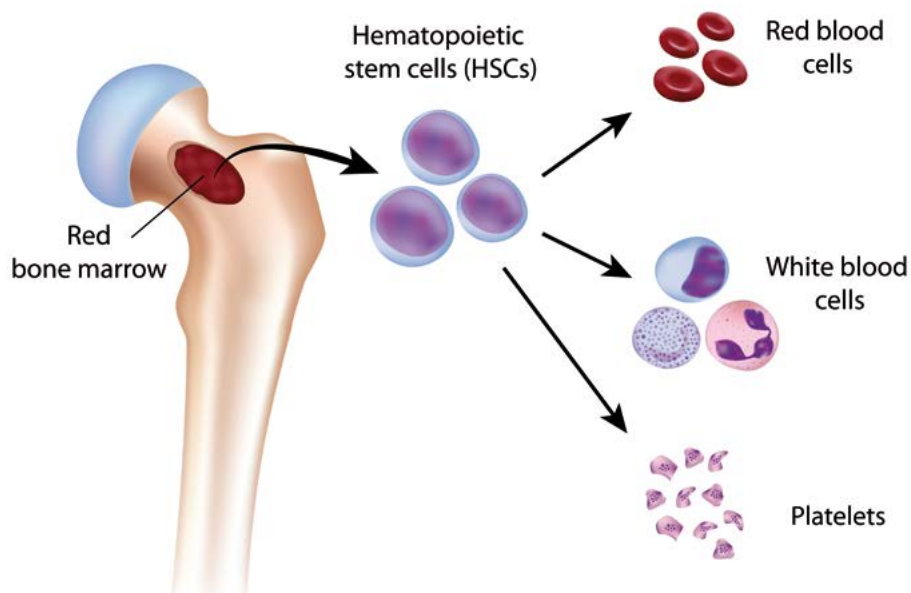


2. Multiple myeloma

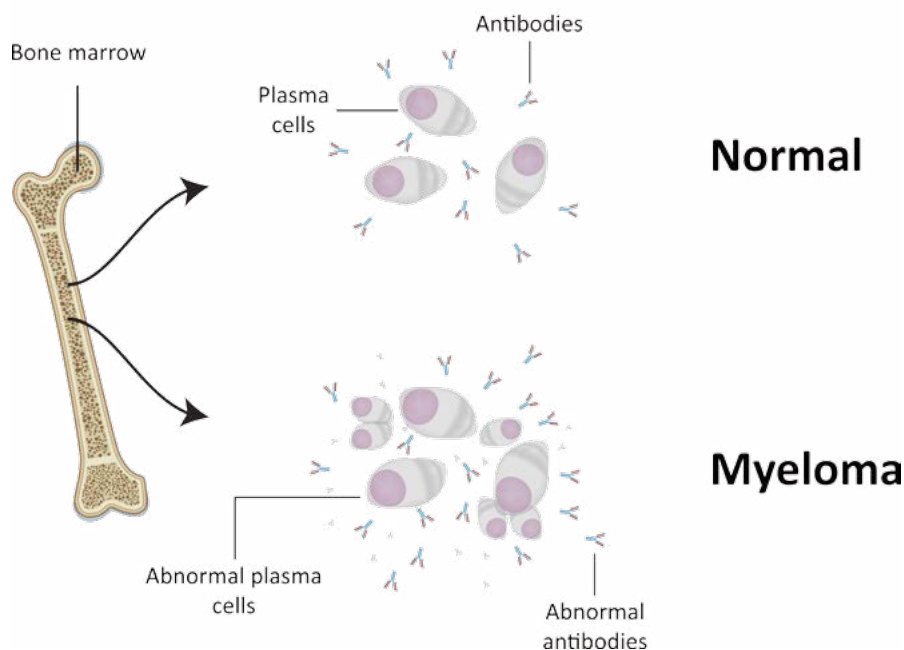
2.1 What is bone marrow and what does it do?

To understand what is happening in myeloma, it helps to look first at the bone marrow and the way it works normally.

The outside of bones is very hard and dense, but the inner layer of larger bones, like the spine, skull, pelvis, shoulders and the heads of long bones, is made of flexible, spongy bone marrow. These are the areas usually affected by the symptoms of myeloma; the small bones of the hands and feet are not normally affected. Because it affects many parts of the body, the condition is also known as multiple myeloma.



Myeloma



Bone marrow is the production site for red and white blood cells and blood platelets – the three main types of cells that circulate in the blood. One type of white blood cells are known as plasma cells. These produce antibodies (immunoglobulins) to fight infection, and are an important component of the body's immune system.

Antibodies are made up of two different kinds of proteins, called heavy chains (which are larger) and light chains (smaller). An antibody has a Y-shaped structure made up of two identical heavy chains and two identical light chains. There are five different types of heavy chains, called G, A, M, D or E; they are usually described as IgG (standing for immunoglobulin G), IgA, IgM, IgD or IgE. Your myeloma will be described by the type of heavy chain detected; IgG myeloma is the most common. The light chains are either κ (kappa) or λ (lambda).

2.2 What is multiple myeloma?

MMyeloma does not cause tumours like many other types of cancer. Instead it causes damage to DNA during development of the plasma cells in the bone marrow, causing them to divide uncontrollably. The abnormal plasma cells, or myeloma cells, release only one type of antibody, known as paraprotein or M-protein, which is also made up of heavy and light chains but has no useful function. Sometimes groups of myeloma cells can accumulate in soft tissues outside the bone marrow, and these are known as plasmacytomas.

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The build-up of myeloma cells in the bone marrow prevents enough normal blood cells from being produced. Together with the presence of paraprotein in the blood and urine, that is the cause of most of the symptoms of myeloma. Measuring the amount of paraprotein present in the blood is useful in diagnosing myeloma or monitoring its progress.

In about 20% of people with myeloma, the abnormal plasma cells only produce the 'light chain' part of the paraprotein structure, and this condition is known as light chain myeloma, or Bence Jones myeloma. In about 1% of myeloma patients, no paraprotein or light chains are produced, and this is non-secretory myeloma.

Myeloma causes symptoms that need treatment for a period, followed by a period of remission where symptoms subside and do not need any treatment. This cycle of remission and recurrence (relapse) often occurs several times over.

2.3 What causes myeloma?

For most people with myeloma, the exact causes are not clear but are thought to be a combination of genetic and environmental factors. Some of the factors that may be implicated are viruses, radiation, exposure to specific chemicals and a generally weakened immune system.

Myeloma is slightly more likely to occur if a family member also has it, which suggests there may be an inherited susceptibility. However, other environmental factors must also be present before myeloma will develop.

Although the exact cause of myeloma is not known, quite a lot is known about the factors which are linked with an increased risk of myeloma, although many patients are not affected by any of these:

- **Age, gender and race:** Myeloma is more common with increasing age. It is about twice as common in people of African origin than in white or Asian people, and three men are diagnosed with myeloma for every two women
- **Family history:** People with a parent, sibling or child who has myeloma are up to twice as likely to develop myeloma as those who have not
- **Obesity:** a risk factor for myeloma
- **Exposure** to toxic chemicals and radiation
- **Autoimmune disorders**, e.g. rheumatoid arthritis and multiple sclerosis
- **Viral infections**, e.g. hepatitis, HIV and herpes.

2.4 What are the symptoms?

Myeloma is a complex cancer with both physical and emotional effects. Not everyone has all of the symptoms, but the following are the most common physical effects. The emotions and feelings that can arise, starting from diagnosis, are discussed in section 3.1 and Chapter 6.

- **Pain:** Most myeloma patients will unfortunately suffer a dull, aching pain at some stage due to the abnormal activity in the bone marrow. Myeloma bone disease most often affects the middle or lower back, the rib cage or the hips, and movement can be painful.
- **Anaemia:** The reduction in the number of red blood cells, which carry oxygen throughout the body, results in anaemia. This can cause fatigue, weakness or shortage of breath, and can result either from the myeloma or as a side-effect of treatment.
- **Fatigue:** overwhelming tiredness is very common. It is often linked with anaemia rather than the myeloma itself; or it can be a side-effect of treatment. Fatigue can affect your ability to work, or limit how well you are able to move about independently.
- **Fractures:** bones are more likely to break in people with myeloma; particularly the spinal vertebrae and ribs.
- **Recurring infection:** myeloma patients have a greater risk of infection, because their immune system is not working properly and there is a lower-than-normal level of white blood cells.
- **Unexplained bruising:** due to a low level of blood platelets.
- **High blood calcium (hypercalcaemia):** calcium can be released into the blood on the breakdown of bone, raising the blood calcium level higher than normal. This can cause thirst, nausea, vomiting, confusion or constipation.

2.5 Stages and types of myeloma

It is now recognised that people who develop myeloma have previously had (although not necessarily been diagnosed with) a condition called monoclonal gammopathy of undetermined significance (MGUS). This typically is shown by people with a raised level of paraprotein, but no other symptoms like bone disease or a higher than 10% level of abnormal plasma cells in the bone marrow. Even if there are up to 30% of abnormal plasma cells (that is, a higher level than in MGUS), this level can rise very slowly and still show no symptoms; a condition known as smoldering myeloma.

Neither MGUS nor smoldering myeloma need treatment, but patients will be monitored at

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least once a year. Not all MGUS patients go on to develop myeloma; the cause of the change to myeloma is not yet understood but is probably genetic.

2.6 Incidence of myeloma

Myeloma is rare, accounting for 1% of all cancers and 15% of blood cancers, but it is the second most common blood cancer after non-Hodgkin's lymphoma.

In Europe about 40,000 people were diagnosed with myeloma in 2015, and this number is predicted to increase to almost 46,000 by 2025².

Myeloma can affect adults of any age, but it is much more common in people aged over 65³ years, and in men rather than women⁴.

2.7 Prognosis

Even though there is still no cure for myeloma, the new drugs developed in the last decade are improving myeloma survival faster than for any other kind of cancer.

Myeloma is affected by many different factors, so it is impossible to predict how long an individual person is likely to live. This will depend on the exact nature of your individual myeloma and any complications. About 40% of patients in England live for at least 5 years, and between 15-19% will live for at least 10 years.

The coming of new drug treatments has meant that myeloma is increasingly being seen by the medical profession as a chronic disease which people survive.

² IARC GLOBOCAN. Estimated cancer incidence, mortality and prevalence worldwide in . http://globocan.iarc.fr/Pages/burden_sel.aspx

³ IARC GLOBOCAN, ibid. http://globocan.iarc.fr/old/burden.asp?selection_pop=62968&Text-p=Europe&selection_cancer=17270&Text-c=Multiple+myeloma&pYear=3&type=0&window=1&submit=%C2%A0Execute%C2%A0

⁴ IARC GLOBOCAN, Ibid. Estimated cancer incidence, mortality and prevalence worldwide in 2012. http://globocan.iarc.fr/Pages/fact_sheets_population.aspx



3. Diagnosis

3.1 Coping with a myeloma diagnosis

Everyone reacts in their own way to being diagnosed with myeloma. Most people feel a sense of shock, and some may feel overcome or numb – all of these feelings are completely natural. Some feel a slight relief, because at last they have found an explanation for how they have been feeling, and find it better to know than just to worry. This is a very natural reaction too.

The diagnosis might make you feel angry – why is this happening to me? – or frustrated in case things are slipping out of your control. As a little time passes, though, you will find that most aspects of your life and activities will stay the same. Many people with myeloma comment that it has made them re-appraise what is most important to them, and have become closer to their partners, family and friends.

A diagnosis of myeloma, as for any type of cancer, often prompts questions about how long you can expect to live. This is very hard to answer, as it is so difficult to estimate how well you are likely to respond to treatment. In the last ten years, many new treatments and combinations have become available, and some people find that a particular treatment works better than others. Today, myeloma patients can expect to enjoy a good quality of life for many years; although unfortunately as yet there is no permanent cure.

It can be very helpful to find out more information about myeloma, so that you understand more clearly what your diagnosis means, and so that you are able to formulate what you need to ask your doctors. It will also help in talking with your family, as they will also be trying to understand more about it. Take your own time to find out about myeloma, as it is easy to become overwhelmed. If you look for information sources on the internet, it's



important to keep to reliable sources from medical organisations, rather than websites where you find opinions which may not be reliable. Remember also that the information you find online should supplement, and not replace, the advice and guidance from your medical team, which is designed for you as an individual.

It can feel very difficult to explain to the people close to you that you have myeloma. It may help if you tell one or two, and ask them to explain it to the other people you feel will need to know. Some people find it easier to tell people by phone rather than face-to-face.

Talking about myeloma with those closest to you can be a great source of support and help, and stops you feeling isolated. Your partner, family and friends may also be feeling anxious about you and perhaps afraid in case they upset you by asking too much. It does help to talk, not just about myeloma but about everyday things as well. Myeloma specialist nurses, who you will meet through your consultant, also have a good understanding of what you are going through and can help you come to terms with your feelings.

3.2 Early diagnosis and smoldering myeloma

We have seen that some people can have up to 30% of abnormal plasma cells in the bone marrow and a raised level of paraprotein in the blood, but no other physical symptoms.

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This is smoldering myeloma, which progresses slowly and will eventually develop into active myeloma. In most cases it does not need treatment, but patients will be monitored at least annually and should have blood tests 3-4 times a year. During this time it is important to watch out for pain, fatigue and weight loss, and to report these symptoms to your doctor.

About one in ten patients diagnosed with smoldering myeloma will develop active myeloma in the first year after diagnosis. About 3% will develop active myeloma in the following year and about 1% each year after that.

Smoldering myeloma is often diagnosed when a blood test taken for other reasons reveals a high level of overall protein in the blood, which will then be investigated further. A blood paraprotein level of 30g/L (grams per litre) or higher (or urinary protein of 500mg in 24 hours or higher), together with a level of 10% or higher of abnormal plasma cells in the bone marrow, indicate a diagnosis of smoldering myeloma. There will be normal kidney function, no anaemia, no bone lesions and a normal level of blood calcium.

While no treatment is given for most smoldering myeloma patients, as the benefit is outweighed by the potential side-effects, a small proportion of patients can be at a high risk of developing active myeloma within the next 1-2 years. Active research is going on at this moment to establish what causes this higher risk. For these patients, early treatment may be beneficial and can delay progression to active myeloma. Treatment may be recommended if the level of plasma cells in the bone marrow, or of free light chains in the blood reach a high level, or if an MRI scan shows areas of bone abnormality.

3.3 Diagnostic tests

A diagnosis of myeloma is reached after a number of measurements and techniques which together present a picture of what is happening in your body. Many of these will be repeated regularly to monitor the progress of the myeloma. The diagnostic tests developed recently enable the doctors to diagnose and treat myeloma at an earlier stage than has previously been possible; i.e. before it has caused complications.

3.3.1 Lab tests

These focus on measuring the level of blood cells and the amount of abnormal protein (paraprotein) and other substances in blood and/or urine.

A full blood count measures the amount of the various types of cells in the blood. Red blood cells are responsible for carrying oxygen around the body; a low level relative to the normal range indicates anaemia, which can make you feel tired and lacking in energy.

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White blood cells are responsible for fighting infection, so a relatively low level means you may be at increased risk of infection. A low level of blood platelets, the third main type, increases the risk of bruising or bleeding.

As well as measuring the blood cells, diagnostic tests will also measure the concentration of protein, waste products and calcium in the blood. The amount of albumin, the main protein in the blood, is lower than normal in people with myeloma, and the amount of beta-2 microglobulin ($\beta 2M$) is higher; this is a key indicator of myeloma. The presence of paraprotein, which is not normally present, is indicative of myeloma and can be measured in the blood or urine.

Calcium levels in the blood are higher than normal in people with active myeloma, as calcium is released from the bone. Urea and creatinine, which are waste products normally removed from the blood by the kidneys, may reach higher levels in the blood if the kidneys are not functioning fully.

Further information about paraprotein can be gained by measurement of the relative amounts of specific parts of the paraprotein structure in the blood – the free light chains. Paraprotein can have one of two types of light chains, known as kappa (κ) or lambda (λ). The total amount of light chains is higher than normal in myeloma, and the ratio between the two types is different. This test can also be done if myeloma is suspected but no paraprotein can be detected. It is also particularly useful for detecting light chain myeloma or non-secretory myeloma.

3.3.2 Imaging tests

It is important that your doctors have a clear picture of any effects the myeloma may have had on your bones, so part of the diagnostic procedure will be to use one or more imaging techniques in a skeletal survey. This is a series of X-rays of your spine, skull, upper legs and upper arms, and will show any areas affected by myeloma bone disease. Any areas where the bone has been damaged can then be repaired.

More information can be obtained from other types of imaging techniques. A CT scan (computerised tomography, sometimes called a CAT scan), is one in which a series of X-ray pictures are combined by computer to build up a detailed picture of particular areas of the body. Sometimes a dye is injected into a vein to help distinguish the different organs.

MRI (magnetic resonance imaging) uses radio waves instead of X-rays, and the radio waves passing through the body are converted by computer into cross-sectional pictures. MRI scans are useful for locating any abnormalities that are not shown up by X-rays.

A PET scan (positron emission tomography) detects plasmacytomas. A small amount of radioactive glucose is injected, and this tends to concentrate in the areas where the cells



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are using the most energy, which is where the abnormal cells have collected. The PET scanner then detects these areas.

PET scans can be integrated with CT scans and conducted at the same time, giving a more complete picture than either method can alone.

3.3.3 Bone marrow aspiration, biopsy and FISH testing

Bone marrow tests are carried out to find out whether abnormal plasma cells are present in the bone marrow, and in what proportion to normal plasma cells.

Samples are taken from the liquid of the bone marrow (bone marrow aspiration) and the solid part (bone marrow biopsy). Both are usually taken by needle from the hip bone, under local anaesthetic. The samples are examined under the microscope by a pathologist, who is trained in evaluating cells and tissues. Normal bone marrow contains less than 5% of (normal) plasma cells. Myeloma patients may have between 10-90% of abnormal plasma cells.

Another type of bone marrow testing to assist in the diagnosis of myeloma is recommended in recently updated guidelines from the International Myeloma Working Group of the International Myeloma Foundation⁵. This is called FISH testing (fluorescence in situ hybridisation).

The test is carried out on a small part of the same bone marrow sample as the biopsy. It is able to identify specific genetic abnormalities in the DNA of plasma cells which were formed when the cells were developing. These genetic changes (mutations) occur spontaneously and the type of mutation indicates whether the myeloma should be treated as standard risk or high risk.

3.4 Understanding the test results

There is no single test which determines whether or not you have myeloma. Instead, the team of haematologists, radiologists, nurse specialists and others will assess the results of the tests described above, and decide if you have myeloma, what type it is and how far advanced. Myeloma is a complex disease, needing input from many medical specialists, so other consultants, like orthopaedic (bones) or renal (kidney) specialists may be involved,

⁵ International Myeloma Working Group (IMWG) Criteria for the Diagnosis of Multiple Myeloma, 29 October 2015. <http://imwg.myeloma.org/international-myeloma-working-group-imwg-criteria-for-the-diagnosis-of-multiple-myeloma/>

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depending on your individual needs.

The test results enable the doctors to find out where the myeloma is in the body and how far it has developed already – known as its stage. Once this is established, decisions can be made on what treatment is needed.

For every different measurement made on your blood, bone marrow or urine, there is a range of values which would be expected in people who do not have myeloma. You may prefer not to know how your own test results compare with these normal ranges. However, many people do find that as their treatment progresses, it can be encouraging to see how their test results are improving with treatment.



4. Treatment

4.1 The aim of treatment

Treatment of myeloma has three key aims: to stop or slow the progression of myeloma, to encourage and prolong the stable periods (remissions), during which only monitoring is needed, and to improve quality of life, e.g. by relieving symptoms.

4.2 How is myeloma treated?

At the time of diagnosis, you may not be experiencing any symptoms at all – this is asymptomatic or smoldering myeloma. Patients with symptoms, or those who are likely to develop symptoms in the near future, need treatment.

Many different types of medication are available. The exact choice will depend on many factors, including how old and how fit or unfit you are. Younger patients who are relatively well will be offered higher doses of drug treatments, followed by intensive treatment with chemotherapy to eliminate the abnormal plasma cells, and stem cell transplantation to replace them with healthy stem cells. People aged over about 70, and those who are less able to tolerate the side-effects of intensive treatment, are more likely to be given a combination of drugs but no chemotherapy or stem cell transplant, although a transplant is possible provided it is with their own cells (see section 4.2.3). This is because any side-effects of intensive treatment would be harder to cope with. Other types of treatments, such as radiation therapy and surgery, may be needed according to particular circumstances.

Treatment comes in phases, which are described in the following sections.

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4.2.1 Active surveillance

If you have smoldering myeloma, your treatment will simply consist of active surveillance, which means being watched closely. Your doctor may recommend starting treatment if you are at risk of developing symptoms within 18 months to two years. Before that, if your bone density is relatively low and you have any indications of bone damage (osteoporosis or osteopaenia), you may be prescribed bisphosphonates to slow it down.

If you have been diagnosed with MGUS (monoclonal gammopathy of unknown significance), you will also be monitored regularly for any health changes.

4.2.2 First-line treatment

The first step – known as first-line treatment or induction therapy – aims to control the myeloma quickly and relieve the symptoms. It will involve treatment with a combination of drugs, including some which have been introduced in recent years and have drastically improved myeloma treatment. Combinations of these have been found to be more effective than single drugs. A typical combination will include:

- A chemotherapy drug to kill the myeloma cells (cyclophosphamide, melphalan or doxorubicin)
- A steroid to suppress inflammation (dexamethasone or prednisolone)
- One or more of the newer anti-myeloma treatments including thalidomide (Thalidomide), lenalidomide (Revlimid) and pomalidomide (Pomalyst) which enhance the performance of the chemotherapy drugs by boosting the immune system and preventing myeloma cells from surviving. Bortezomib (Velcade) and carfilzomib (Kyprolis) target cells actively producing proteins, principally the abnormal plasma cells.
- Pain relief as needed; usually non-steroidal anti-inflammatory drugs (NSAIDs).

If you are newly diagnosed, combinations you might be prescribed are:

- Cyclophosphamide – dexamethasone – thalidomide (CDT), or
- Melphalan – prednisolone – thalidomide (MPT) or
- Melphalan – prednisolone – Velcade (VMP).

In some cases, induction therapy can remove all abnormal plasma cells, which is called a complete response or complete remission. However treatment will need to be continued, as without it, the myeloma would return.

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The length of time for which you will need to take the drug combination will be somewhere between 4-6 months, depending on how you respond. The drugs are usually taken for a few days or weeks, followed by several days or weeks without treatment, and then repeating the cycle. This is to allow time for the healthy cells, which may have been damaged by the chemotherapy, to recover. Not everyone will respond to any one combination of drugs, so you will be monitored and another combination can be chosen if the one you have started does not appear to be working for you.

4.2.3 Intensive vs maintenance treatment

After this period of induction therapy, a decision will be made on what comes next.

If you are well and in complete remission, and myeloma is your only medical condition, the most likely course is a stem cell transplant with intensive chemotherapy.

If you are not very well, or aged over about 70, it is likely that you will not be given a transplant but instead will be offered continued consolidation drug therapy. Both types of transplant will be followed by a prolonged period of maintenance drug therapy.

4.2.4 Relapse treatment

We have seen that some combination drug treatments may not be effective for particular people, and it may be necessary to try a different combination. This is a relapse, and it will occur to everyone with myeloma; often several times. It will be picked up in the results of the diagnostic tests (e.g. your paraprotein level) which you will continue to have regularly. You may also feel that your pain or tiredness are becoming worse.

It is understandably disappointing, but there is no reason why another treatment should not work better. It is not a reason to be over-anxious, but it will probably mean a change to the medication you are taking. For some people, a treatment that worked well earlier can be repeated with good results. The same reasoning applies when a treatment that has been effective, no longer appears to work so well (known as refractory myeloma).

The first time a relapse happens, most people will be given bortezomib (Velcade). This is given by injection under the skin, once or twice a week. It is usually given in combination with the steroid, dexamethasone, and often with chemotherapy agents, cyclophosphamide or melphalan.

The drug most often given at a second relapse is lenalidomide (Revlimid); usually in combination with dexamethasone and cyclophosphamide. Alternatively, it may be possible to have a second stem cell transplant, if you have had a good long period of remission since the first one.

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Alternatively, it may be possible to have a second stem cell transplant, if you have had a good long period of remission since the first one.

Carfilzomib (Kyprolis) is approved in both the US and Europe for treatment following a third relapse, providing patients have previously had at least two cycles of treatment with bortezomib and either lenalidomide or thalidomide, and the disease has become worse in the 60 days since the end of treatment.

A number of other new treatments have recently been approved or are under consideration for use following relapse or for refractory myeloma:

<p>Panobinostat (Farydak)</p> <p>as a third-line treatment in combination with bortezomib and dexamethasone</p>	<p>Elotuzumab (Empliciti)</p> <p>in combination with lenalidomide (Revlimid) and dexamethasone.</p>
<p>Ixazomib (Ninlaro)</p> <p>in combination with lenalidomide (Revlimid) and dexamethasone for patients with relapsed or refractory myeloma and at least one prior treatment</p>	<p>Daratumumab (Darzalex)</p> <p>as a single agent for patients who have already had three lines of therapy</p>

Further details of these new drugs are given in section 7.1.

4.2.5 Stem cell transplants

a. Autologous transplants

If you are well and in complete remission, and myeloma is your only medical condition, the most likely course is a stem cell transplant using your own cells (called an autologous stem cell transplant or auto-SCT). It involves collection of stem cells from your bone marrow at the end of induction therapy, and is possible in older, fit people.

The first step is drug treatment to stimulate production of stem cells and their movement from the bone marrow into the blood. In the actual transplant, given in hospital, blood is

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passed through an apheresis machine which separates it into its different components. The stem cells can be removed and all the other components are returned to the body. The stem cells are frozen and retained for use in transplants – usually enough for two occasions.

A relatively high dose of the chemotherapy drug melphalan is then given, followed about two days later by the stem cells, which will move into the bone marrow and start to develop into new blood cells. The process can take several weeks, during which it is essential to avoid infection. It is common to feel unwell during this time, and several more weeks of convalescence may be needed after you leave hospital. The great advantage of transplants is that patients usually respond very well and can achieve a long remission period.

b. Allogenic transplants

In relatively rare circumstances, younger, fit people can be offered a transplant of stem cells from other close relatives; usually a brother or sister. This is known as an allogenic transplant. It makes use of the donor's stem cells to boost the immune response of the person with myeloma, by developing into specialised blood cells that can attack the abnormal plasma cells. This is believed to be the reason why allogenic transplants have a lower rate of relapse than autologous transplants.

There is a problem, though, as an allogenic transplant carries the risk of graft-versus-host disease (GVHD), in which the donated cells attack patient's healthy tissues as well as the abnormal plasma cells. A lower-risk allogenic transplant can be considered, in which a lower chemotherapy dose than usual is given.

The transplant is followed by high-dose chemotherapy with melphalan, and recovery over a period of weeks.

4.3 How is treatment response measured?

How well you have responded to treatment will be measured regularly in terms of the amount of key substances or cell types in your blood, and of other substances in your urine. Your doctors will be particularly interested to measure the level of paraprotein or light chains in your blood; the number of abnormal plasma cells in the bone marrow, and an improvement in your symptoms, kidney function and general wellbeing.

Doctors will often categorise your response to treatment according to the levels of these indicators, from 'stringent complete response' (no paraprotein in blood or any abnormal plasma cells in bone marrow), through 'complete response' and then 'partial response' to 'stable disease' and 'progressive disease' (getting worse). Stable disease means that although there has been less than 50% reduction in paraprotein, it has plateaued at a stable level, so this is a good outcome as well as remission.



5. Coping with physical aspects

5.1 Dealing with myeloma symptoms

As well as the treatments to control the myeloma itself, there are many other ways to help you cope with the symptoms and to avoid developing complications. There is a certain amount of overlap between symptoms of myeloma and side-effects of treatment, so the following sections explain the symptoms you may encounter, although you are most unlikely to have them all. It may be helpful just to refer to the symptoms and treatments outlined in this section as and when you need to, rather than trying to take in, everything that could possibly happen all at once. In any case, keeping a watch on your general health, and keeping your doctor informed of any changes, will help greatly.

Infection is harder to fight if you have myeloma, so do watch out for signs like a raised temperature, sore throat, nausea, vomiting or diarrhoea. You should contact your doctor if your temperature goes above 38°C. You may be given antibiotics or antivirals to treat the infection or intravenous antibodies (immunoglobulins) to boost your immune system.

5.2 Dealing with side effects of myeloma treatments

5.2.1 Anaemia

Anaemia is a common problem with myeloma due to a reduction in the number of red blood cells. This leads to a feeling of weakness, lack of energy and continuing tiredness. The bone marrow and its capacity to produce red blood cells can recover with myeloma treatment, so the anaemia does

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not always need to be treated itself. If it does need treatment, you can be given a blood transfusion to restore the level of red blood cells quickly. Alternatively, erythropoietin (EPO) can be given to stimulate production of more red blood cells.

5.2.2 Appetite loss

Sometimes you may have a sore mouth from chemotherapy, or simply don't feel like eating and a meal replacement drink may be useful.

It can be easier to eat smaller meals, more often than usual, and take a larger meal when you feel able to. Avoid fatty or fried foods and those which are very sweet or spicy. It is important to keep drinking water or other drinks – milk, squash, decaffeinated tea or coffee, ideally up to three litres (five pints) each day, or ordinary tea or coffee in moderation.

If these approaches don't really help, you can ask to be referred to a dietician who can recommend some more alternatives.

5.2.3 Blood problems (see also 5.2.16)

The presence of a large amount of paraprotein in the blood of myeloma patients can cause it to thicken (it becomes hyperviscous). This can slow down the passage of blood to the brain and cause dizziness, confusion or even symptoms similar to those of a stroke. You or someone near you should call for medical help if these symptoms occur. It can be treated quickly by a technique called plasmapheresis, which takes blood from a vein and separates the blood cells from the liquid (plasma) component containing the paraprotein, which is discarded. The blood cells are mixed with replacement plasma from a donor and returned to your blood system.

Myeloma can also increase your risk of a blood clot (which could present a risk of deep vein thrombosis or pulmonary embolism), especially if you are taking thalidomide or lenalidomide (Revlimid) in combination with high-dose steroids or chemotherapy drugs. You will be assessed for your risk if you are starting on thalidomide or lenalidomide, or if you need to go into hospital, and treated if necessary with an anticoagulant like warfarin or fondaparinux.

5.2.4 Constipation

This can arise as a result of too high a level of calcium in the blood, from the breakdown of bone. It can also be a side-effect of treatment with thalidomide or bortezomib, or it could be linked with compression of the spinal cord due to bone damage in the vertebrae. It is important to take advice, to find out the cause. Don't be afraid or embarrassed about telling your doctor about constipation,

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as they are quite used to this sort of problem and will be able to help resolve what can be a distressing problem with a big impact on your quality of life.

It is much easier to prevent constipation occurring than to treat it, so it is a good idea to make sure that your diet includes some foods which are high in fibre, e.g. bran, wholegrain bread, fruit, vegetables and especially beans or lentils. Cake and white bread should be kept to a minimum; also sugar-rich foods in general. It is also important to make sure that you don't become dehydrated, and most people need to drink between 2-3 litres of water every day. That sounds a lot, but it includes water in tea and coffee. There are also a number of natural remedies which may help, including seeds, syrup of figs and bran husks, but it is advisable to check with your doctor in case of any interaction with your medication. Finally, gentle exercise like walking, swimming or cycling should be a regular part of your routine.

If constipation becomes a big problem, your doctor can prescribe several types of laxative, which either reduce the removal of water from the faeces in the intestine, making them softer, or increase their bulk, or stimulate the movement of the bowel.

5.2.5 Diarrhoea

Diarrhoea is considered as episodes of passing loose or watery bowel motions more than three times a day. It can be accompanied by headache, stomach cramps and loss of appetite or even nausea and vomiting. Some anti-myeloma drugs e.g. bortezomib (Velcade) can cause diarrhoea, or it can result from an unrelated infection.

Diarrhoea can also arise if you have AL amyloidosis as well as myeloma.

AL amyloidosis is a disorder which involves production of an abnormal protein (amyloid) in the bone marrow. AL amyloidosis can occur as a separate condition but can also be identified after a diagnosis of myeloma. It results in an excessive production of light chains (see sections 2.1 and 2.2), which become bound together into fibrils within the tissues and organs, disrupting the way they work and giving rise to symptoms including diarrhoea.

Whatever the cause of your diarrhoea, you should report it to your doctor or nurse so the most appropriate treatment can be prescribed. There are also several things you can do yourself which will help. You should make sure to drink plenty of water or diluted fruit juice and avoid tea and coffee. Keep to small, light meals including chicken, eggs and white fish, and avoid spicy foods.

5.2.6 Dysphagia

Some people with myeloma suffer from difficulty in swallowing solids, liquids or both, which is known as dysphagia. This may be associated with coughing or choking while eating or drinking.

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The cause is not quite clear but may be related to the blood viscosity being raised because of the paraprotein it is carrying. The chance of dysphagia also seems to increase after receiving a stem cell transplant.

Treatment depends on the symptoms experienced, but avoiding meat (which can be hard to swallow) may help, and also therapy can help to reduce the chance of choking.

5.2.7 Fluid retention

Myeloma is characterised by excess light chain production and a high level of blood calcium; both of which can damage the kidneys. Acute kidney failure (known as myeloma kidney or cast nephropathy) is often the first symptom of myeloma, which can sometimes severely reduce the kidney's capacity before detection. It is caused by the excess light chains blocking the kidney tubules, causing them to fail in their function of removing waste substances from the blood.

Chronic kidney failure develops over a longer period (weeks or months) and is shown by the presence of light chains in the urine and a rise in creatinine in the blood. It is caused either by cast nephropathy, or by deposition of amyloid protein in patients with amyloidosis. The urine shows a high level of albumin, and the blood has a very low level. Fluid retention follows, causing swelling in the legs, ankles or feet.

Renal failure is usually treated by dialysis and about 20% of myeloma patients need this treatment. Kidney transplantation is not usually available to myeloma patients. It is important in treatment of myeloma to prevent the occurrence of kidney failure rather than to treat it, and useful guidance is to avoid dehydration (to keep the kidneys actively functioning) and to avoid non-steroidal anti-inflammatory drugs (e.g. ibuprofen). Bisphosphonates (especially zoledronic acid and pamidronate disodium) should be used with caution as these can make kidney problems worse.

5.2.8 Fatigue

Fatigue is a very common symptom of both myeloma and its treatment. It is often made worse by anaemia. Your tiredness can make even routine tasks feel too difficult to attempt, but a number of approaches can help.

It's important to get enough sleep, so try to make a routine of going to bed and getting up at the same time, and take a rest in the daytime when you need to. Gentle exercise can help by improving your appetite and your energy level.

When you need to do particular tasks, spread them out in time and don't try to do everything at once; focus on whatever is most important or urgent. Accept offers of help from your family and

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friends – as well as helping you, this will make them feel that they are really being useful. If you are working, investigate whether you could work from home or reduce your hours or responsibilities.

5.2.9 Hair loss

Most chemotherapy drugs used in treating myeloma cause hair thinning rather than complete loss, which is mainly related to the intensive chemotherapy given before a stem cell transplant. It happens because the chemotherapy drugs attack all the cells in the body which are rapidly dividing, and among these are the hair follicles. Hair loss can be distressing, but the hair will grow back within a few months after the treatment is completed. Your new hair may be finer than before, or more curly, or a slightly different colour.

Having your hair cut short before you start to lose it through chemotherapy can work well, as you can feel more of a sense of control while it is thinning and growing back. Otherwise, today's wigs are very natural-looking, or you could use a scarf – and many people choose not to cover their heads at all. It's entirely a matter of what feels right for you.

5.2.10 Infertility

If you are hoping to have children in the future, you need to know that some myeloma treatments can affect fertility by affecting the function of the ovaries or of sperm production, and to take advice from your doctor. This infertility is often temporary, but could be permanent depending on which drugs you are given. Those most likely to affect fertility are cyclophosphamide and melphalan, and permanent infertility is more likely with higher doses, like those given just before a stem cell transplant. Infertility can also arise from radiotherapy of the pelvic area.

If this is important for you, your doctor can refer you to a fertility specialist to

discuss what can be done. It may be possible to undergo sperm or egg collection for later use, and fertility counsellors can provide supportive advice.

5.2.11 Nausea and vomiting

A high level of calcium in the blood (hypercalcaemia), side effects from chemotherapy drugs and also unrelated infections can all give rise to nausea and vomiting. While very unpleasant symptoms, they can be treated. If they are a side-effect from the drugs, e.g. bortezomib (Velcade), they can be treated with anti-emetics. If infection is the cause, antibiotics may be needed. Hypercalcaemia is more serious as an excess of calcium in the blood can cause kidney damage, and this is treated with intravenous fluids and anti-myeloma drugs.

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As well as drug treatment, it can be helpful to eat small, frequent meals and to avoid food that is fatty, spicy or has a strong smell.

5.2.12 Neutropaenia

If you have a relatively low level of white blood cells (neutrophils) in your blood, which can happen especially after chemotherapy, you could be at greater risk than normal of food poisoning caused by bacterial or fungal contamination. The shortage of neutrophils, which would normally counteract these agents, is called neutropaenia. The risk is also increased because the lining of the gut can be damaged by chemotherapy and radiotherapy, which makes it easier for bacteria in food to enter the bloodstream.

If you develop neutropaenia, you will be given detailed advice by your doctor or dietician on which foods to avoid and which are good alternatives. The strictness of this advice depends on your level of neutrophils. You may need to continue following this guidance even after your neutrophil count has recovered, as you may still be at a higher risk of infection.

The main foods to avoid are unpasteurised dairy products (like farm-fresh milk); soft or blue cheeses; raw or lightly-cooked shellfish; raw, undercooked or smoked meat, poultry or fish; raw or undercooked eggs or foods that contain them, like sauces or ice-cream; foods, drinks and supplements described as 'probiotic' or 'bio', and meat or vegetable pates.

You will also need to follow a high level of food safety hygiene practices in everything related to your food – shopping, food preparation and storage. There are many points to take into account, and you will be given detailed guidance, but for example: avoid buying food with damaged packaging and avoid large packets that will be open for longer and increase the chance of contamination. Always store raw and cooked foods separately and make sure that frozen food is defrosted covered and at the bottom of the fridge (rather than at room temperature), to avoid it dripping onto other food. Cook all food thoroughly until it is piping hot all through and meat juices run clear. Take care with hand hygiene: always washing hands before preparing food and after touching your hair, pets, rubbish, dirty laundry and visiting the toilet. Keep a separate chopping board for raw meat or fish and do not use it for other foods.

5.2.13 Pain

You should also tell your doctor if you are feeling more bone pain than can be controlled by your painkillers – there are alternatives and you should not feel that you have to put up with it. Be especially aware of increased or sudden back pain, or tingling or loss of sensation in your legs, and tell your doctor. It may help to keep a record or diary of how you are feeling so you can describe it clearly at your next visit or if you contact an out-of-hours doctor.

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5.2.14 Peripheral neuropathy

Peripheral neuropathy means damage to the peripheral nervous system, which means all the nerves in the body except the brain and spinal cord. These nerves communicate between the brain and the other parts of the body and are composed of two types of specialised cells: motor neurons and sensory neurons. The motor neurons carry electrical impulses from the brain to the muscles and enable them to carry out movement by contracting or relaxing. The sensory neurons carry information about the sensations of pain and touch to the brain from all external parts of the body. When these sensory neurons are damaged in peripheral neuropathy, the sensory messages can be distorted or interrupted, which the brain interprets as tingling, numbness, altered sensation, increased sensitivity to touch, or pain. The sensations are most often felt in the hands and feet.

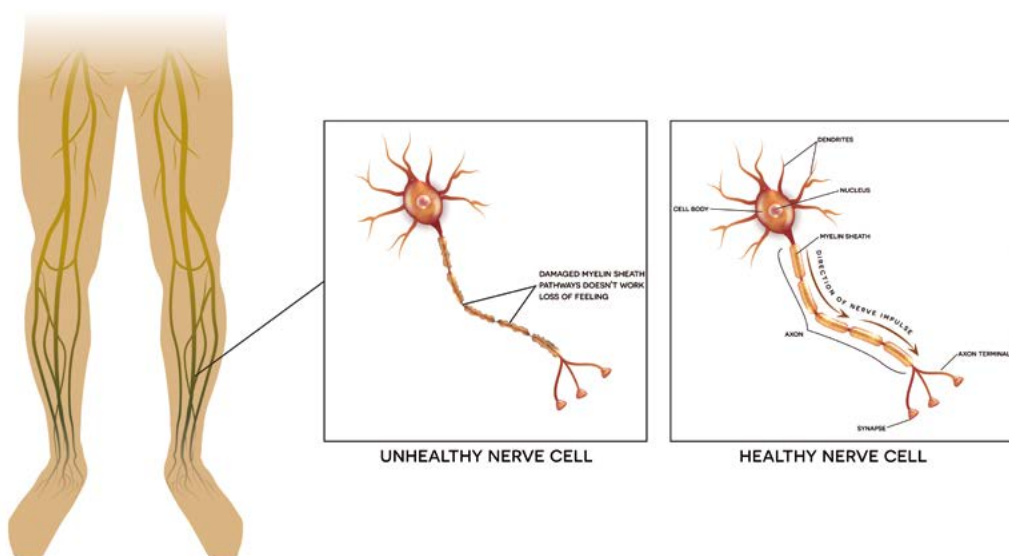
Peripheral neuropathy is present in a small proportion of patients when they are diagnosed with myeloma, but about four out of five will develop its symptoms to some extent later; either through myeloma itself through deposits of paraprotein in the nerve cells, or as a side-effect of treatment. Thalidomide, bortezomib (Velcade) and vincristine can all contribute to peripheral nerve damage.

The treatment for peripheral neuropathy depends on what has caused it. If it is caused by myeloma, then the myeloma treatments themselves should reduce the neuropathy. If it has arisen as a side-effect, then the treatment concerned can be stopped or given at a reduced dose. If it is a side-effect of bortezomib (Velcade), it may be sufficient to change from intravenous to subcutaneous administration (injection into the skin rather than into a vein).

Pain from peripheral neuropathy can be relieved by a range of drugs including amitryptiline, gabapentin or carbamazepine; by local anaesthetic or by a TENS machine (transcutaneous electrical nerve stimulation) which delivers tiny electrical impulses to the nerves in the skin.

PERIPHERAL NEUROPATHY

NERVE DAMAGE



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5.2.15 Skin conditions

Thalidomide and bortezomib (Velcade) can result in a rash and dry, itchy skin rashes, or more rarely, thalidomide can cause a more serious rash with blistering. If this happens, the medication should be reduced or withdrawn.

It is worth also being aware of shingles, which is a viral infection to which myeloma patients are more susceptible than other people. Shingles is an infection of a nerve and the skin around it, and causes an itchy, painful rash that is normally on one side of the body; on the chest, abdomen or face. The rash forms blisters which eventually burst and crust over. Shingles can be treated by antiviral tablets (aciclovir, valaciclovir or famciclovir), which work best if started in the early stages. Calamine lotion will relieve itching and has a cooling effect, or a cloth soaked in cold water will soothe the blistered skin but should be stopped once the blisters have stopped oozing.

5.2.16 Spinal cord compression

Myeloma bone disease involves the breakdown of bone more quickly than it can be repaired. If this happens in the spine or ribs, even minor pressure can cause the bone to fracture. A break in one or more spinal vertebrae can cause the vertebrae to collapse and is sometimes the cause of compression of the spinal cord and loss of height. The symptoms of spinal cord compression are sudden back pain and loss of sensation in the legs, and it may also involve incontinence, inability to pass urine, or constipation.

Urgent treatment is needed, and one of two surgical procedures may be needed. In percutaneous vertebroplasty, a type of bone cement is injected into the vertebra, which stabilises the joint and reduces pain. The other, known as balloon kyphoplasty, involves inserting a small inflatable balloon into the vertebra before the cement is injected. In some cases this can also restore height and correct any spine curvature, as well as relieving the pain.

5.2.17 Thrombocytopaenia

The production of abnormal plasma cells in the bone marrow leads to a lower production of other blood cells, including blood platelets. These are involved in blood clotting, so if you have a relatively low level of platelets in your blood, you can be more prone to bleeding or bruising. It can also occur as a side-effect of myeloma treatments, including thalidomide, bortezomib (Velcade), lenalidomide (Revlimid), cyclophosphamide and melphalan.

The condition is known as thrombocytopaenia, and it may give no symptoms at all, or spontaneous bleeding from the gums or nose, extended bleeding from cuts, excessive bruising or a red rash of tiny pinpoint marks, commonly in the lower legs.

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Your regular total blood count (see section 3.3.1) will monitor any changes in the level of blood platelets. The condition will improve gradually as a result of your myeloma treatment, and the bone marrow will become better able to produce platelets. If the thrombocytopaenia is a side-effect of treatment, it may be necessary to reduce the dose or delay treatment until your platelet level recovers.

You should keep a watch for any unusual bleeding and report it to your doctor. It is also a good idea to avoid anything that could give rise to bleeding or bruising, and to use a soft toothbrush to avoid damaging your gums. Limiting alcohol intake is helpful, as alcohol tends to reduce the platelet level and 'thin' the blood. If you see blood in urine, stools or vomit, this should be reported immediately.

5.3 Caring for yourself

5.3.1 Talking to your doctor

It is important to talk with your doctor and nurses about myeloma and how it is affecting you. You need to understand fully what the diagnosis means, how your treatment is planned, and what you are likely to experience in the coming months and years. Ask your doctor about the aims of each treatment in your treatment plan. Myeloma is a chronic disease, and how it affects you will change as time goes by, so you need a good idea of what to expect.

In order that they can provide the right treatment and ease any pain or discomfort you may be experiencing, you need to tell the doctors and nurses about any symptoms, even if they seem unimportant like nausea or constipation. There are many ways in which they can help you be more comfortable, but this can't happen if you keep these things to yourself. Don't be afraid to share things that are bothering you; however small. Having a clear understanding of what you are experiencing will only help the medical professionals to get a full picture of the progress of your myeloma and how well your treatment is working.

5.3.2 Diet and nutrition

A healthy, high-calorie diet with a high amount of protein will help to keep you active, prevent you feeling tired, and also help to fight infection. Eat a wide range of foods but include plenty of fruit and vegetables, poultry, fish and wholegrain bread. Make sure you drink enough water and other drinks to keep the kidneys working well (up to three litres a day), but it is a good idea to limit your intake of alcohol.

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5.3.3 Physical activity and exercise

It is good to take what gentle exercise you feel able to, as this will reduce the loss of calcium from your bones and help you feel less fatigued.

Exercise will help to keep you fit, strengthen muscles and will also give a good feeling that you are looking after yourself. Walking, swimming and aqua-fitness are all helpful, as are exercise regimes like yoga and tai chi. Gym training is also helpful, providing you have the approval of a physiotherapist or sports trainer before you start, and that you warm up and cool down carefully before and after exercising to avoid muscle strain.

The greatest obstacle to taking exercise if you have myeloma is that your bones will be weakened. Strengthening your muscles will help to take the pressure off your bones, but exercise should be started very gently and gradually increased. If you have any pain, stop doing whatever caused it and only do what is comfortable. Contact sports, where you might easily knock into another person or sports equipment, should be avoided.

Plenty of rest and avoiding stress if at all possible will also help to keep you in good health.

5.3.4 Sexuality

Many medical conditions affect how patients feel about themselves and to lose interest in sex is not at all uncommon. Sometimes this can be because you feel too tired or in too much discomfort, and anxiety can also make sex something that just doesn't appeal, at least at present. Alternatively, the cause may be a physical response to one or more of your medications. Not wanting to engage in sex can itself cause more stress between partners, if you feel depressed or unattractive, or if you or your partner feel unwanted or rejected.

It's important to talk with your partner, so that you understand each other's feelings and to make sure that neither of you misinterprets the situation. Once you start to talk, you should be able to find out what level of physical contact feels right for the time being, and then gradually develop that into a fuller intimacy when you are ready. Your doctors and nurses can also offer guidance and support; and they will not be embarrassed if you ask for help.

5.3.5 Oral care

Because your immune system is weakened if you have myeloma, you may be more susceptible to various mouth problems and infections, like cold sores or thrush. Good dental hygiene, using a soft toothbrush, and keeping yourself well hydrated by drinking plenty of water are the best ways to prevent infection in your mouth. Any pain or discomfort in your mouth should be reported to your doctor or nurse, and can be relieved with antibiotic or pain-killing mouthwashes or by specific

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antifungal or antiviral treatments. You should avoid foods which increase the soreness through being salty, spicy or acid.

Myeloma treatments, especially at high doses, can make you more likely to have mouth ulcers or an inflamed mouth lining. Some other treatments can temporarily lower your blood platelet count (see section 5.2.17), and this can make you more liable to bleed from your gums. You may find that your mouth stays rather dry – this is because many myeloma treatments interfere with saliva production, and this can be relieved with an artificial saliva spray.

Pain in or damage to the jawbone (osteonecrosis of the jaw) is a very rare complication which may be linked to treatment with bisphosphonates and triggered by tooth removal. If you are about to begin bisphosphonate treatment, it is a good idea to have a dental checkup and any invasive dental treatment done first. Despite this very small risk, it is important for everyone with myeloma routinely to be treated with bisphosphonates to protect them from myeloma bone disease.

5.3.6 Active ageing

People who have myeloma are usually 65 or older. That means you can benefit from all that has been learnt in the last 20 years on the many general ways that all older people can benefit in health and wellbeing.

Active ageing is an idea that has been recognised by the world's most influential organisations, including the World Health Organisation, the United Nations Economic Commission for Europe and the European Commission, and all these and more have developed guidance and recommendations. The basis of initiatives to support active ageing is helping people to remain physically and mentally active and independent, with a good quality of life for as long as possible and if possible, to contribute to the economy and to society. It is much more than a question of having a healthy diet and keeping up some form of exercise.

There will be times during your treatment for myeloma when you don't feel able to be very active, and then you must of course be guided by your doctor and nurses, and your own body. But myeloma is a relapsing-remitting disease, which means that you can expect to have long spells when the myeloma is stable and you can carry on virtually all of your normal activities, or even find new ones. There is now significant evidence that people who try to maintain social activities benefit from better health, a greater feeling of support from others and a better feeling of wellbeing and self-esteem.

Apart from working, which is considered in the next chapter, you might find new enjoyment in many activities that are helpful to anyone in retirement, such as voluntary work, learning a new skill or developing an existing interest for which you have never had enough time before. An enormous number of life-long learning programmes are now available online for older people; many of which include local classes or visits. All of these will help you keep active, involved and interacting with like-minded people, and will use your knowledge and experience.



6. Coping with emotional and social issues

6.1 Dealing with the treatment

6.1.1 Before treatment

The exact treatment which your doctor recommends will depend on the results of all the tests that were carried out at and immediately after diagnosis. Understanding what is happening to you and why it is needed will help you to cope, both at the outset and as your treatment proceeds.

Before you start treatment, it is important to ask your doctor what the treatment options are, how effective they are likely to be and what side effects you may encounter. Every patient will respond slightly differently, so it is impossible for doctors to tell you exactly how you will react, but it is possible to give a good general indication. They will also be able to tell you what is likely to happen if you decide not to have a particular treatment.

6.1.2 During treatment

Make sure you tell your doctor or nurse if you have any new symptoms or if your existing symptoms get worse, so that your treatment can be modified or changed if necessary. Most side-effects of treatment are short-lived and can be reduced with supportive treatment. It is also important to find out from your doctor about any developments which would mean that you should call for medical help during your treatment.

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While your active treatment is under way, it can be easy to feel that what you are going through is hard to bear. Living with myeloma is much more of a challenge than simply enduring the symptoms and side effects of treatment, since it will inevitably interfere with at least some of your normal activities. You may feel a sense of loss of time and freedom to do what you want. At times this can make you feel depressed, angry or resentful. You may feel isolated and that other people don't understand what you are feeling or are afraid to talk with you about it. All of these feelings are completely natural, and they will recede as you start to respond to your treatment. Try to think positively and do things you enjoy, but don't feel guilty if some days are not so good. Joining a myeloma support group or online forum can be enormously helpful in sharing advice and keeping up your morale.

6.1.3 Once treatment is finished

Once your treatment period is over, you should be feeling much better and able gradually to take up your normal life activities again. In some countries and some cases, maintenance treatment, e.g. a low dose of thalidomide, is given over a long period with the aim of making the period of remission last as long as possible. In other instances a consolidation treatment can be given for a short time after the end of the main therapy to obtain the maximum benefit. Both of these options may be beneficial, but there is still not enough evidence and not everyone will benefit from them.

If you have not responded to your treatment as well as anticipated, or if the myeloma stops responding in a relatively short time, this is known as refractory myeloma. It can be very disappointing, but it does not mean that you will not respond to a second-line course, usually of a different treatment. An indication that a treatment has not been successful is a return or increase of symptoms, including bone pain and lack of energy. The relapse will be confirmed by tests; principally a rising level of paraprotein in your blood. The second-line treatment will usually include a steroid and either bortezomib (Velcade) or lenalidomide (Revlimid). Try to keep positive, as a repeat or different treatment will often return the myeloma to a stable phase and there are many treatment options to be tried.

6.2 Preparing for medical check-ups

You will have regular check-ups from the time of your diagnosis – the frequency may vary in different countries of Europe but they are likely to be every few weeks and will be set by your physician. Because myeloma is a complicated condition and you may want to ask about many aspects of your symptoms, feelings and treatments, it is a good idea to think carefully about it before your check-ups, so you can make sure to cover everything.

If you leave a notebook somewhere handy in your house or carry it with you, you can make a note of questions whenever they come into your mind. You can take the list with you to the doctor at your check-up. Many people find that it is helpful to take their partner or friend with them, to

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help you to take in and remember the doctor's suggestions. If he or she proposes a change in your treatment, it is perfectly acceptable to ask for a little more time to make your decision when you have been able to discuss it with your family.

6.3 Managing work and myeloma – Practical issues for patients and families

If you are able to continue working, that will help you to maintain involvement and a sense of purpose, and give you all the social interaction that comes from being part of an organisation. When you have been diagnosed with myeloma, you will need to contact your employer and come to some arrangement, as you may well need to take time off for tests and treatments; possibly involving staying in hospital. Your doctor or nurse should be able to provide a written confirmation of your diagnosis which will explain how it may affect your ability to work. Many employers are becoming more flexible about hours and conditions, and it may be possible to investigate reducing your hours and reducing your level of responsibility if that would help.

If you normally look after someone else who is dependent on you, like children or elderly parents, it is sensible to make some other plans for their care. You may not need to put the plans into action, but it is possible that you may need to go to hospital at short notice for treatment or care, e.g. if you have an infection. If that should be needed, it will help if you don't have to make urgent decisions about caring for others at that time.

6.4 Insurance, financial and other issues

Insurance is an important issue if you plan to travel, in case you become ill while you are in another country. It is sensible to discuss your plans with your doctor if you are likely to be undergoing treatment at the time you plan to travel.

If you are travelling within the European Economic Area⁶ or Switzerland, you can benefit, free or at a reduced cost, from the same health care services as are available to residents of those countries, by obtaining a European Health Insurance Card. This is free of charge and can be obtained online. However, while this will cover your medical care costs, it will not cover the cost of returning you to your own country, so individual travel insurance is strongly recommended. Insurance for travel to countries outside Europe, especially in North America, can be very expensive.

⁶ The European Economic Area consists of the 28 member states of the European Union (Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the UK) PLUS Iceland, Liechtenstein and Norway.

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Being treated for myeloma may mean that you need to take a significant amount of time off work or leave it permanently, which can give rise to financial worries. You may also need to spend an increasing amount of money on medications and travel to hospital appointments, which can make a difference as well.

In many countries you may be eligible for a number of benefits from the government, which will help to alleviate financial pressure. These vary according to the individual country, but in many cases provide for a living or personal independence allowance, support to pay for a carer to look after you, or a tax allowance. If you are working, you may be entitled to a statutory support allowance if you are not eligible for sick pay from your employer. A relative or friend looking after you may be able to claim a carer's allowance.

Advice on the various benefits available to you can usually be obtained from nurses and social workers at your hospital, or from community / citizens' advice bureaux or online.



6.5 Advance decisions – living wills

Many people find it helpful to think in advance and make some plans about whether they would prefer to refuse particular types of treatment at some time in the future. Where this is written down in a document it is known as a living will or advance decision. Its purpose is to make your wishes clear if you are unable to communicate yourself. Because it is a legal document, there are some differences in the requirements of individual countries. The following paragraphs explain the purpose of the advance decision; but you will need to check exactly what the provisions are in your own country.

The document must explain exactly which treatments you want to refuse, and in what circumstances (if you might not want to refuse them in all situations). It can be helpful to discuss with a doctor what treatments you might need in future, and what would happen if you refuse them. If you might die as a result of refusing such treatment, the document must state clearly that the advance decision is to apply to the specific treatment even if life is at risk or shortened as a result. An advance decision cannot be used to ask for specific treatments, or to ask for help to end your life.

To make your wishes legally valid, they must be written down and signed and dated by yourself and by a witness. To be put into action, your wishes must be applicable to your situation and the treatments available, if you are not able to make your own decisions about your treatment, e.g. if you are unconscious, and if there is no reason to suspect that you might have changed your mind since the document was signed.

6.6 Getting help and looking for resources

You can find help and information from many sources. First and foremost, your own medical team – should be your main reference source as only the members of this team have full knowledge of your individual condition and what treatments are working or have been less successful. This team will include your consultant haematologist, specialist nurses and general practitioner. Depending on your exact combination of symptoms, you may also be advised by specialists in particular systems of the body, e.g. a renal specialist if you have kidney problems, or a neurologist if you have neuropathy. You should also have access to social workers or a community advice bureau for questions relating to social care or finance.

You may find that information from the internet is variable in its quality and level of detail, and also healthcare systems are slightly different in every country. An excellent starting point for information relevant to your own country is the website of your own national myeloma association, or Myeloma Patients Europe. Many of these associations can put you in touch with support groups in which you can talk and exchange experiences and problems with other myeloma patients and also professionals. Some have online discussion forums, where you can chat with patients wherever they live. Details of how to find the associations are given in the Appendix.



7. New insights and future directions

7.1 New targets and coming drugs to treat myeloma

The development in the last ten years of the newer anti-myeloma treatments including thalidomide (Thalidomide), lenalidomide (Revlimid), pomalidomide (Pomalyst), bortezomib (Velcade) and carfilzomib (Kyprolis) has greatly improved the prospects and quality of life for people with myeloma. A number of others have shown promising results in recent trials, although not all are yet authorised for use. These include:

- Panobinostat (Farydak); approved in both the US and Europe for use in combination with bortezomib and dexamethasone, for patients who have had at least two prior standard therapies, including bortezomib and an immunomodulatory agent.
- Elotuzumab (Empliciti) was approved for use in the US and Europe to be used in combination with lenalidomide (Revlimid) and dexamethasone in patients who have received one to three prior therapies, but no particular type of previous therapy is specified.
- Ixazomib (Ninlaro) was approved for use in the US and Europe to be used in combination with combination with lenalidomide (Revlimid) and dexamethasone for patients who have had at least one prior therapy.
- Daratumumab (Darzalex); approved in both the US and Europe as a single agent to treat patients with myeloma who have received at least three prior treatments.

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Attention has turned now to the genetic changes causing myeloma and influencing their response to treatment. Individual patients vary significantly, and even one person can respond differently to a medication if it is given at different stages in their myeloma. This might be one reason why patients sometimes fail to respond well to a drug which was helpful earlier in their illness, or vice versa., Recent advances in genetic analytical techniques are now enabling these genetic alterations to be detected. The gene sequence responsible for myeloma has now been completely mapped by the Multiple Myeloma Genomics Initiative of the Multiple Myeloma Research Foundation. The next 5-10 years are likely to see an upsurge in these discoveries being brought into clinical trials, leading to a clearer understanding of how treatments can be tailored to individual patients. Further studies of these differences will eventually enable treatments to be adjusted and developed to suit individual patients, based on their gene sequences.

As myeloma is relatively rare, patients unfortunately do not always have access to the same standard of care available wherever they live. For example, university hospitals in major cities have myeloma specialists who may be engaged in current drug trials and are fully aware of the latest findings on the uses and advantages of innovative treatments. Patients of rural, local hospitals are often in the care of general haematologists or oncologists who may not be fully informed on the latest research developments, clinical trials and complexities of myeloma. In some countries, patients have little chance to participate in clinical trials of new treatments that could offer them improved treatment or reduced side-effects. Continuing research into myeloma is urgently needed, as it is important that recent myeloma research findings in these centres are quickly translated into treatments that are available to more myeloma patients.

7.2 What are clinical trials?

Clinical trials are a series of studies progressing from small pilots to large-scale trials, which evaluate and compare new medications, combinations of medications, procedures and medical devices and generate information on how safe and effective they would be in practice. Satisfactory results of clinical trials are required by both national and European regulatory agencies before the products or procedures can be granted market authorisation and all the conditions of use agreed. The trials are carried out according to strict procedures (protocols) which have been approved by an independent research ethics committee to protect the interests of people taking part.

Before a new medication can enter the market and be available to patients, its safety and efficacy must be tested throughout the phases outlined below. Volunteer patients can take part in the trials of new medications, provided they meet the specific conditions of the individual trial, which may include the current state of their myeloma, recent treatments and their outcome, age, other health conditions etc. Many people with myeloma are keen to participate in trials, because as well as giving access to new treatments before they are widely available, taking part will guarantee a high level of monitoring from the clinical staff running the trial.

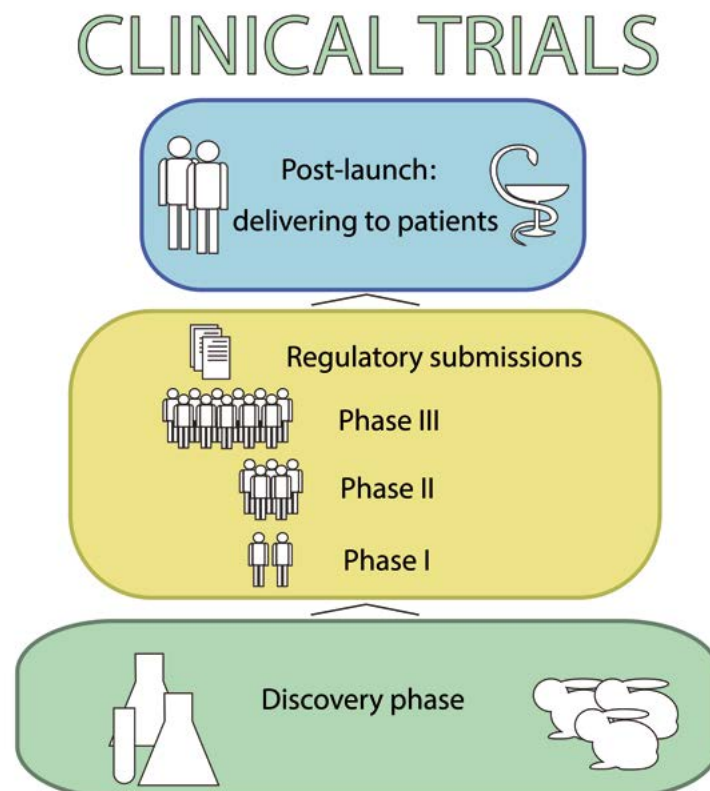
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Clinical trials are usually carried out in hospitals, and often take many months or years to collect all the results. They could be funded by a public sector research body, a private foundation (e.g. the International Myeloma Foundation) or research- funding organisation (e.g. the Multiple Myeloma Research Foundation or the European Myeloma Network), or by a pharmaceutical company. In the later phases, trials are often carried out simultaneously at a number of different study locations – which gives patients an increased chance to take part.

Clinical trials in the EU are regulated by the requirements of the EU clinical trials regulation⁷ which is designed to ensure that no harm comes to the participants in trials and that the outcomes are scientifically validated. The regulation replaced earlier EU requirements which had to be implemented by national legislation; often leading to different interpretations in the different countries. The intention of the clinical trials regulation was to encourage more clinical trials to be conducted in Europe by reducing the differences between the regulatory requirements of different countries.

⁷ Regulation (EU) No 536/2014 of 16 April 2014 on Clinical trials on medicinal products for Human use, and repealing Directive 2001/20/EC. OJL 158 of 27.5.2014, 1-76



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7.2.1 Phases

Phase I studies are usually small, involving less than 50 patients and are focused on safety. They aim to identify the best route of administration, identify any side effects and identify the best dose to avoid or minimise the unwanted effects.

Phase II trials will be conducted on products or treatment which have already successfully completed Phase I, and typically involve up to 300 patients. Larger numbers are needed to make sure that the result is statistically reliable, as different people may respond in different ways to the same treatment, due to their individual genomics. Phase II concentrates on establishing efficacy – whether the product or treatment works, using the dose and route established in Phase I. Products which are already in use, but are being tested in a new combination or approach, will start with Phase II.

For medications which are intended to treat myeloma, researchers will need to evaluate whether the myeloma responds to treatment, whether and by how much the periods of remission can be extended, whether and by how much survival can be prolonged, and whether there is improvement in general quality of life. All these parameters will be compared with the benefit gained from existing treatment, as the overall aim is to find out if the new product or treatment is better than treatments that are already available.

Phase III trials will follow, if a critical proportion of patients show improved benefit from the new treatment compared to existing treatments, and if the side effects are tolerable. Phase III trials can often involve several thousand patients, and they aim to confirm the safety and effectiveness of the new treatment, in comparison to that of 'control' patients given the existing (standard) treatment. Allocation of patients to either the new treatment or the control group is randomised, and if possible the study is 'blinded' so that the patient does not know which group he or she is in, or 'double-blinded' so that neither the patient nor the doctor knows. These precautions help to avoid any natural inclination in either to misinterpret the results.

7.2.2 Inclusion criteria

The protocol for every clinical trial defines its exact purpose, so the researchers have to be sure that the participants meet clear criteria so that the trial results concern only what is being tested and could not be explained by some variation between the participants. The criteria for taking part in a specific trial are known as inclusion criteria. They commonly include age, gender, whether the myeloma is newly diagnosed or relapsed, what treatment has already been given and whether there are other significant medical conditions.

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7.2.3 Informed consent

Before taking part in a clinical trial, you will be asked to sign a form giving your informed consent. This means having a complete understanding of the purpose of the study, the treatments and tests involved, and possible benefits or risks. While many patients are keen to try a new treatment, others might be more concerned about whether it was any better than what they already have, or about new side effects. Giving informed consent means that you have weighed up all these factors and decided to continue.

7.3 Finding out about myeloma clinical trials

Clinical trials currently under way in Europe are all listed on the European Clinical Trials Register, <https://www.clinicaltrialsregister.eu/>. In September 2015, there were 332 myeloma trials taking place.

If you are interested in taking part in a trial, the best person to advise what would be appropriate for you is your own doctor or myeloma specialist. They will also have access to details of current trials near enough for you to take part, what they are testing and if they are appropriate for your own stage of myeloma.

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Appendix – Sources of information and support

Myeloma Patients Europe (MPE) is an umbrella organisation of myeloma patient groups and associations from across Europe. MPE was formed following the merger in 2011 of the European Myeloma Platform and Myeloma Euronet.

Find out about your local myeloma group at www.mpeurope.org/group-locator.

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