

# Myeloma

## A Patients' Guide

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MYELOMA PATIENTS EUROPE

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# 1. Introduction

Although myeloma is the second most common form of blood cancer, it only represents 1% of all cancers<sup>1</sup>. Many people have never heard of this disease, so being given a myeloma diagnosis can be quite frightening. If you have not heard of myeloma before, in some ways it can be more worrying than being told you have another type of cancer.

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 what treatments are under investigation, 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.

<sup>1</sup> IARC GLOBOCAN. Estimated cancer incidence, mortality and prevalence worldwide in 2020 <https://gco.iarc.fr/>

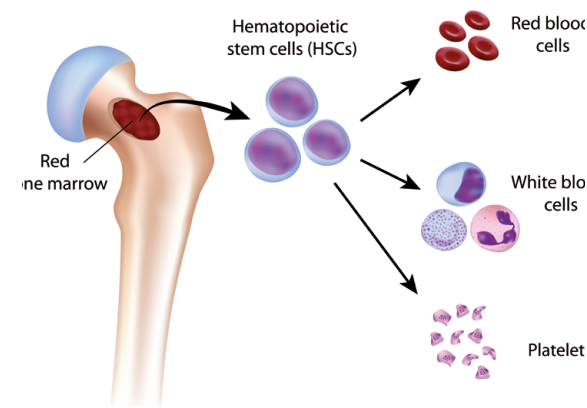
# 2. Myeloma

## 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, are made of flexible, spongy bone marrow. These larger bones are 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.

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 cell is the plasma cell. These cells 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  $\kappa$  (kappa) or  $\lambda$  (lambda).

## 2.2 What is myeloma?

Myeloma is caused by 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 the form of a tumour in soft tissues outside the bone marrow, and these are known as plasmacytomas.

The build-up of myeloma cells in the bone marrow prevents normal blood cells from being produced. The build-up of myeloma cells and the presence of paraprotein in the blood and urine cause 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 may cause symptoms that need treatment. When myeloma doesn't cause symptoms, we call it asymptomatic, indolent, or smouldering myeloma. Smouldering myeloma may or may not be treated depending on the risk of progression to symptomatic myeloma.

The goal of treating myeloma is to achieve a good quality response, so the patient can have a long period of remission. Myeloma may recur several times during the patient's life, in which case it may be necessary to treat it again using different drug combinations.

## 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, although this has yet to be proven. However, other environmental factors must also be present before myeloma will develop.

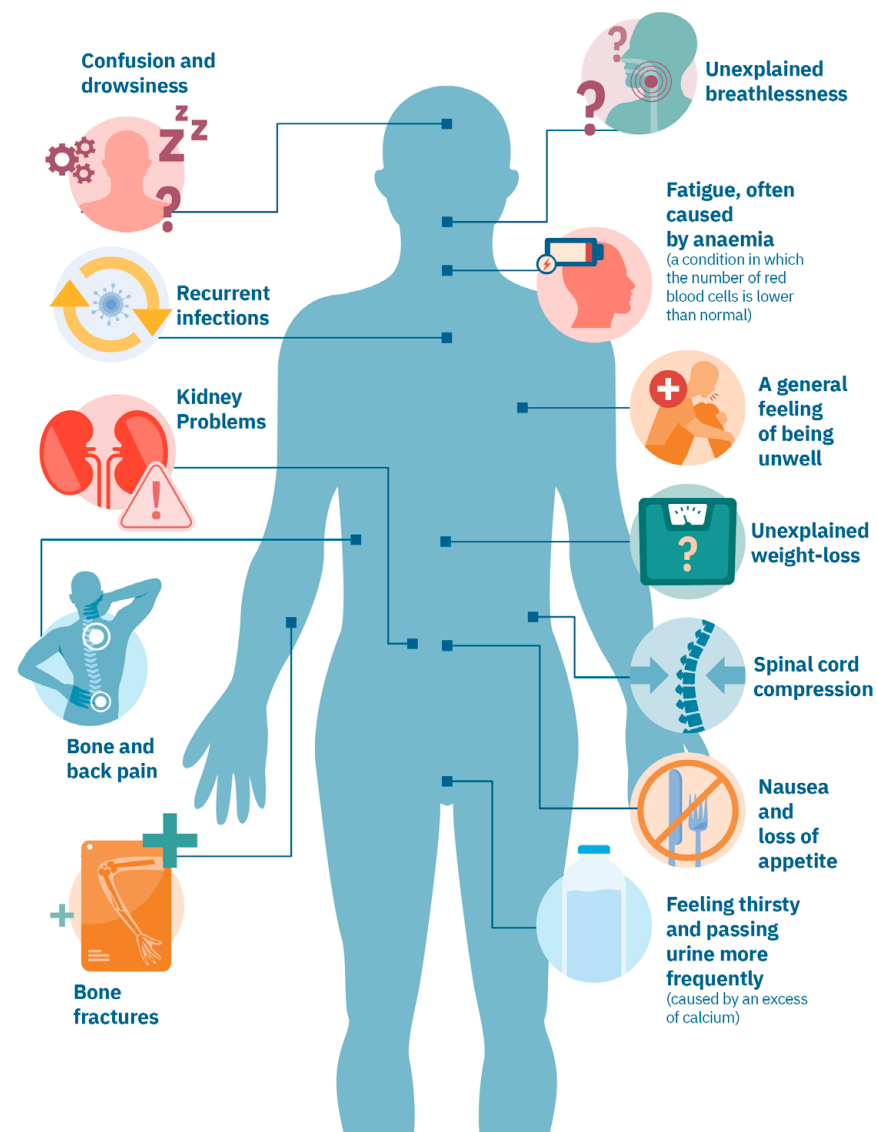
Although the exact cause of myeloma is not known, quite a lot is known about the factors which are linked with an increased risk of myeloma, although many patients are not affected by any of these:

- **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** is considered 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 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 shortness 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; also meaning you may have a higher risk of bleeding.
- **High blood calcium (hypercalcaemia):** calcium can be released into the blood as bone is broken down, therefore 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 is typically seen in 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 smouldering myeloma.

Neither MGUS nor most smouldering myeloma patients need treatment, but patients will be monitored at 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. On the other hand, smouldering myeloma patients will eventually progress to symptomatic myeloma.

## 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 50,918 people were diagnosed with myeloma in 2022<sup>1</sup>.

Myeloma can affect adults of any age, but it is much more common in people aged over 60 years (with the average age of 70 at diagnosis), and in men rather than women. Only 2% of cases of myeloma are diagnosed in people under the age of 40<sup>2</sup>.

## 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, your overall health and any complications that may arise. For example, about 40% of patients in England live for at least five years, and between 15-19% will live for at least 10 years.

The development of new drugs for the treatment of myeloma has meant that it is often seen by medical professionals as a chronic, yet lifelong, disease that people survive.

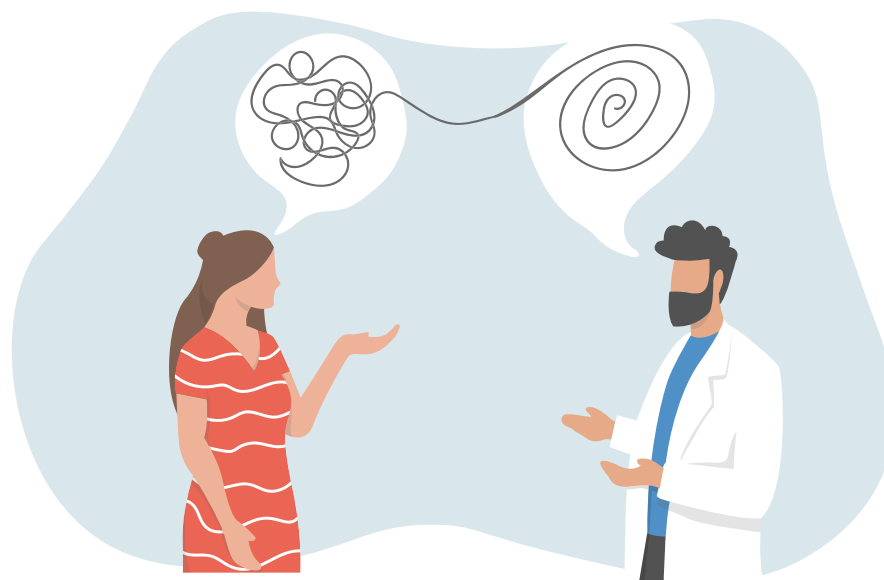
<sup>2</sup>Cancer.net Multiple Myeloma: Risk Factors. <https://www.cancer.net/cancer-types/multiple-myeloma/risk-factors#:~:text=Age,occur%20in%20people%20under%2040.>

# 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 time passes, 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-evaluate 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 10 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, currently 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 are able to formulate what you need to ask your doctors. It will also help to talk with your family, as they too will want to understand more about it. Take your own time to learn about myeloma, as it is easy to become overwhelmed. If you look for information on the internet, it is important to use reliable sources such as medical organisations, rather than websites and forums where you could discover a variety of opinions, many of which may not be reliable. Also remember 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. At first, it may help if you tell one or two of your closest loved ones or friends 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 can prevent you from feeling isolated. Your partner, family and friends may also feel anxious about your health and wellbeing and perhaps afraid to ask you 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 health care journey, 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 smouldering myeloma

Smouldering myeloma (less commonly known as asymptomatic myeloma) is an early form of myeloma, which usually progresses to active myeloma, but may take some time to do so. Smouldering myeloma does not normally cause symptoms, so it is often diagnosed by chance - blood tests may show an increased level of overall protein and this will usually prompt further investigation.

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 10 patients diagnosed with smouldering 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.

Smouldering 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 10-60% of abnormal plasma cells in the bone marrow, indicate a diagnosis of smouldering 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 smouldering 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 ongoing 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 free light chains in the blood, reach a high level, or if an MRI scan shows areas of bone abnormality.

## 3.3 Diagnostic tests

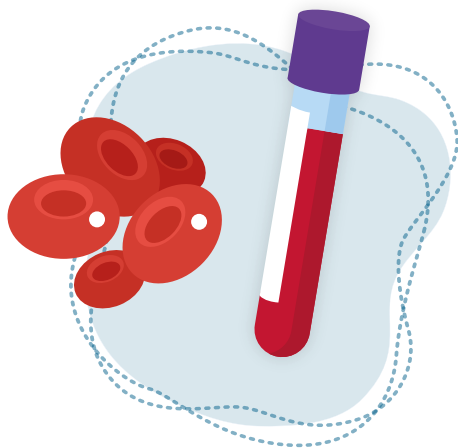
A diagnosis of myeloma is reached following a number of measurements and techniques, which together present a picture of what is happening in your body. Many of these will be repeated regularly to monitor the progress of the myeloma. The diagnostic tests developed recently enable doctors to diagnose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

### 3.3.1 Lab tests

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

A complete 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



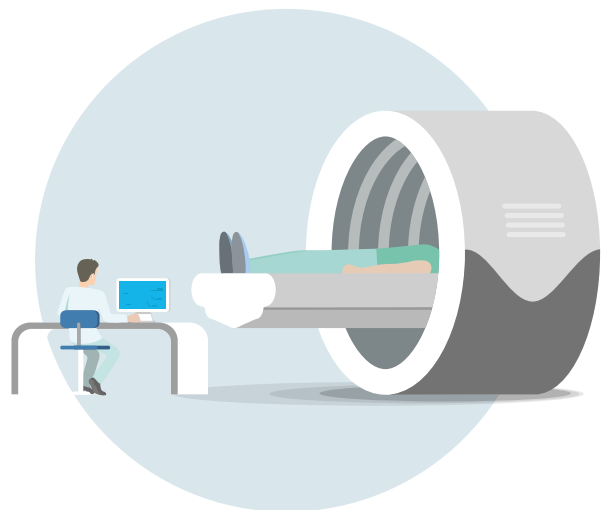


low level relative to the normal range indicates anaemia, which can make you feel tired and lacking in energy. White blood cells are responsible for fighting infection, so a relatively low level means you may be at increased risk of infection. A low level of blood platelets (the third main type) increases 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 during bone breakdown. 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 properly functioning.



Further information about paraprotein can be gained by measurement of the relative amounts of parts of the paraproteins in the blood – known as the free light chains. Paraproteins can have either kappa ( $\kappa$ ) or lambda ( $\lambda$ ) light chains. 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 conducted if myeloma is suspected but paraprotein levels are undetectable. In addition, it is particularly useful for identifying 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. Some areas where the bone has been damaged can be identified for repair to hopefully reduce pain.

More information can be obtained from other types of imaging techniques. A CT scan (computerised tomography, sometimes called a CAT scan), is a type of imaging technique where a series of X-ray pictures are combined by computer to build up a detailed picture of areas of the body. Sometimes a dye is injected into a vein, during a CT scan, to help the doctor reading the images distinguish various organs.

A PET scan (positron emission tomography) detects plasmacytomas, a tumour-like collection of myeloma cells outside of the bone marrow in soft tissues. During this scan, a small amount of radioactive glucose- (sugar) based dye is injected into your vein through a needle. This dye will then concentrate in (and highlight) the areas in the body where cells are using the most energy. This is therefore an indicator of an area where cancerous myeloma cells have collected.

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

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.

### 3.3.3 Bone marrow aspiration, biopsy and FISH testing

Bone marrow tests are carried out to determine 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, a doctor who is trained to evaluate 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 used to assist in the diagnosis of myeloma has been recommended in recently updated guidelines from the International Myeloma Working Group of the International Myeloma Foundation<sup>3</sup>. This is called FISH testing (fluorescence in situ hybridisation).

The test is carried out on a small part of the same bone marrow sample taken during the biopsy. FISH testing can identify specific genetic abnormalities in the DNA of plasma cells that 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 that determines whether or not you have myeloma. Instead, a 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 it is. Myeloma is a complex disease, needing input from multiple medical specialists, therefore, other consultants, like orthopaedic (bones) or renal (kidney) specialists may be involved, depending on your individual needs.

The test results enable the doctors to find out where the myeloma is in the body and how advanced it has become – known as its stage. Once this is established, decisions can be made to determine what treatment is needed, or what treatment combination is appropriate.

<sup>3</sup>Rajkumar S. V. (2016). Updated Diagnostic Criteria and Staging System for Multiple Myeloma. American Society of Clinical Oncology educational book. American Society of Clinical Oncology. Annual Meeting, 35, e418–e423. [https://doi.org/10.1200/EDBK\\_159009](https://doi.org/10.1200/EDBK_159009)

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 smouldering myeloma. Patients with symptoms, or those who are likely to develop symptoms in the near future will likely begin treatment after consultation with their haematologist.

Many different types of medication are available. The exact choice will depend on a combination of 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. Some 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 (see section 4.2.3). This is because any side-effects of intensive treatment would be difficult for frail patients to tolerate. Other types of treatments, such as radiation therapy and surgery, may be needed in specific situations (for example findings of a plasmacytoma close to the spinal cord).

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

#### 4.2.1 Active surveillance

If you have smouldering myeloma, your treatment will simply consist of active surveillance, which means being watched closely. This is usually done with bone marrow biopsies, blood and urine tests, and imaging. 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 osteopenia), 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 or progression.

#### 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 symptoms. It will involve treatment with a combination of drugs, including some which have been introduced in recent years and have drastically improved myeloma survival. 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) and lenalidomide (Revlimid) enhance the performance of the chemotherapy drugs by boosting the immune system and preventing myeloma cells from surviving. Bortezomib (Velcade) target cells actively producing proteins, principally the abnormal plasma cells. Daratumumab (Darzalex) mimics antibodies and targets myeloma cells.
- Pain relief as needed; usually non-steroidal anti-inflammatory drugs (NSAIDs).

If you are newly diagnosed and not eligible for a stem cell transplant, combinations you might be prescribed are (note that not all of these combinations are available in every country. For more information about myeloma treatment landscape, see section 7.1 'Approved treatments for myeloma')<sup>4</sup>:

- daratumumab (Darzalex) – lenalidomide (Revlimid) – dexamethasone (**DaraRd**)
- daratumumab – bortezomib (Velcade) – melphalan – prednisone (**DaraVMP**)

<sup>4</sup>EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up<sup>1</sup>. Annals of oncology, 32(3), 309–322. <https://doi.org/10.1016/j.annonc.2020.11.014>

- bortezomib (Velcade) – lenalidomide (Revlimid) – dexamethasone (VRd)
- bortezomib (Velcade) – melphalan – prednisone (VMP)
- bortezomib (Revlimid) – dexamethasone (Rd)

If you are newly diagnosed and considered eligible for a stem cell transplant, combinations you might be prescribed for your initial or induction treatment before stem cell transplant are (note that not all of these combinations are available in every country)<sup>5</sup>:

- bortezomib (Velcade) – lenalidomide (Revlimid) – dexamethasone (VRd)
- daratumumab (Darzalex) – bortezomib (Velcade) – thalidomide – dexamethasone (DaraVTd)
- bortezomib (Velcade) – thalidomide – dexamethasone (VTd)
- bortezomib (Velcade) – cyclophosphamide – dexamethasone (VCd)

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.

Treatment is usually taken for a few days or weeks at a time with a few days to a week off treatment, although these lengths can vary. This is known as a cycle and is usually repeated over 4-6 months depending on how you respond and what side-effects you may experience. Treatment in cycles 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, or if you are unable to tolerate the treatment.

#### 4.2.3 Intensive vs maintenance treatment

After the initial 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. Consolidation therapy is usually given following a stem cell

transplant once cancer can't be detected. This works to kill any remaining cancer cells that may be left in the body. Maintenance therapy is usually given after a stem cell transplant or after stem cell transplant and consolidation therapy. The maintenance therapy drug is usually given in a low dose over a long time to reduce the risk of relapse in patients in remission.

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. Maintenance therapy might also be used after induction therapy.

#### 4.2.4 Relapse treatment

As some combination drug treatments may not be effective for particular people, it may be necessary to try a different combination. All myeloma patients will experience this at some point in time, and likely several times throughout their disease course, where they undergo a period of remission (or complete removal of plasma cells) and then eventual worsening of their myeloma, usually seen by an increase in paraprotein levels. You may also feel that your pain, tiredness, or myeloma symptoms become worse during a period of relapse.

It is understandably disappointing, but there is no reason why another treatment should not work better. It is also 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 receive another stem cell transplant, but if that is not possible then they will be given a combination treatment with bortezomib (Velcade). This is given by injection under the skin, once or twice a week. Bortezomib (Velcade) is usually given in combination with a steroid, such as dexamethasone or prednisone, along with other drugs such as doxorubicin (a chemotherapy), pomalidomide (Imnovid), or daratumumab (Darzalex<sup>5</sup>). Other options for treatment at first relapse are treatments using lenalidomide (Revlimid) and dexamethasone in combination with drugs such as carfilzomib (Kyprolis), isatuximab, daratumumab (Revlimid), or elotuzumab (Empliciti)<sup>5</sup>.

<sup>5</sup>EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Annals of oncology, 32(3), 309–322. <https://doi.org/10.1016/j.annonc.2020.11.014>

In subsequent relapses, these are various combinations that have been approved in recent years for treatment. Treatment at subsequent relapses will usually depend on if your myeloma is considered refractory (meaning it will not respond) to specific drugs. Some examples of approved treatment combinations used are<sup>5</sup>:

- bortezomib (Velcade) – panobinostat (Farydak) - dexamethasone
- pomalidomide with or without isatuximab – dexamethasone
- daratumumab (Darzalex)
- elotuzumab (Empliciti) – pomalidomide – dexamethasone
- belantamab mafodotin (Blenrep)
- selinexor (Nexpvio)
- idecabtagene vicleucel (Abecma)

Further details on new and up-and-coming drugs are discussed in section 7.2.

#### 4.2.5 Hematopoietic stem cell transplantation (HSCT)

##### a. Autologous transplants (ASCT)

If you are well and in complete remission after initial induction treatment, 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 or ASCT). It involves the collection of stem cells from your bone marrow and is possible in eligible and fit patients.

The first step is drug treatment to stimulate the production of stem cells and their movement from the bone marrow into the blood. In the actual transplant, given in hospital, blood is passed through an apheresis machine, meaning the blood is separated into its different components. During apheresis stem cells are removed and all the other components are returned to the body. The stem cells are then frozen (or used fresh) and used in transplants – usually enough for two occasions can be saved and frozen.

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 recovery 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 (Allo-SCT)

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 or Allo-SCT. 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 the patient's healthy tissues as well as the abnormal plasma cells.

## 4.3 How is treatment response measured?

How well you have responded to treatment will be measured regularly in terms of the number 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 and the number of abnormal plasma cells in the bone marrow, and look for 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 such as the following:

- **Stringent complete response:** no paraprotein in the blood and no abnormal plasma cells in the bone marrow)
- **Complete response:** less than 5% abnormal plasma cells in the bone marrow; and no paraprotein in the blood or urine

- **Very good partial response:** greater than a 90% decrease in paraproteins in the blood or urine
- **Partial response:** a 50-90% decrease in the paraproteins in the blood or urine
- **Minimal response:** a less than 50% decrease in the paraproteins in the blood or urine
- **Stable disease:** although there has been less than a 50% reduction in paraprotein, it has plateaued at a stable level, so this is a good outcome as well as remission.
- **Progressive disease:** worsening of myeloma seen by at least a 25% increase in paraproteins in the blood or urine.

**Minimal residual disease (MRD)** is a newer way to measure disease response and is often used in clinical trials. With the use of specialised tests (flow cytometry, polymerase chain reaction (PCR) and next-generation sequencing (NGS)), the measurement of MRD detects the presence of a small number of cancerous cells in your body that would not otherwise be noticed using traditional testing.



## 5. Coping with physical aspects

### 5.1 Dealing with myeloma symptoms

In addition to treatments directed at controlling your myeloma, there are many other ways to help you cope with the symptoms and 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 it is unlikely you will have them all. It may be helpful to refer to the symptoms and treatments outlined in this section only when you need to, rather than trying to take in everything that could possibly happen all at once. In any case, keeping a close eye on your general health, and keeping your doctor informed of any changes, will help greatly.

### 5.2 Dealing with side effects of myeloma treatments

#### 5.2.1 Anaemia

Anaemia is a common problem with myeloma due to a decrease in the number of red blood cells. This leads to a feeling of weakness, lack of energy and tiredness. The bone marrow and its capacity to produce red blood cells can recover with myeloma treatment, so the anaemia does 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) injections 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 do not feel like eating. In this situation, a meal replacement drink may be useful.

Or 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, decaffeinated tea or coffee, ideally up to three litres (five pints) each day, or ordinary tea or coffee in moderation.

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

### **5.2.3 Blood problems**

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 like those of a stroke. You or someone near you should call for medical help if these symptoms occur. Blood thickening 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 (blood thinner) drug such as warfarin or fondaparinux.

### **5.2.4 Constipation**

This can arise owing to high levels of calcium in the blood from the breakdown of bone. It can also be a side-effect of treatment with thalidomide or bortezomib. It is important to take advice so you can find out the cause. Don't be afraid or embarrassed about telling your doctor about constipation, as they are quite used to this sort of problem and will be able to help resolve something that can be very uncomfortable and have a significant impact on your quality of life.

It is much easier to prevent constipation rather than to treat it, so it is a good idea to make sure that your diet includes some foods that 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 like a lot, but it includes water in tea and coffee. There are also several natural remedies that 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 laxatives, 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 described as episodes of passing loose or watery bowel movements 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) or chemotherapy 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 the 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.

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 that 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. You may also try something known as the B.R.A.T. diet that includes bananas, rice, apple sauce and toast to help counter the diarrhoea.

### **5.2.6 Dysphagia (difficulty swallowing)**

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. The cause is not quite clear but may be related to fatigue and weakness, or the blood viscosity being raised because of the paraprotein it is carrying. The risk 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 and kidney failure

Myeloma results in high levels of paraprotein in the blood and a high levels 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 to filter even before damage has been detected. Kidney failure is caused by the excess light chains blocking the kidney tubules, causing them to fail, thus making them unable to remove waste substances from the blood.

Chronic kidney failure develops over a longer period (weeks or months) and is shown by the presence of light chain proteins in the urine and a rise in creatinine in the blood. Chronic kidney failure is caused either by cast nephropathy, or by deposition of amyloid protein in the kidneys, in patients with amyloidosis. In chronic kidney failure, urine tests show a high level of albumin, while in blood tests, albumin levels are low. Low albumin levels in the blood make it difficult for fluid to stay in the blood vessels, so it then flows into the soft tissues, causing swelling in the legs, ankles or feet.

Kidney failure is usually treated by dialysis and about 20% of myeloma patients need this treatment after some time. Kidney transplantation is not usually available to myeloma patients. It is important in the 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 several approaches can help.

It's important to get enough sleep, so try to develop 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 over 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 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 curlier, 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. As an alternative, today's wigs are very natural-looking, or you could use a scarf – many people choose not to cover their heads at all. It's whatever 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 changing the function of the ovaries, or of sperm production, and should 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 Keratopathy or visual changes

Some of the newer treatments for myeloma, such as belantamab mafodotin (Blenrep) have an associated side effect called keratopathy. This is a result of the drug itself binding to cells on the surface of the eye and causing cystic-like changes. These changes can usually be seen on examination by an ophthalmologist and may or may not be associated with symptoms. If you do have symptoms such as blurred vision, difficulty seeing, dry eyes, or eye pain, you must let your haematologist know immediately, as they may need to adjust the dose or delay a dose of your medication. Also, you must have an eye examination before starting treatment with belantamab mafodotin (Blenrep) and frequently while on treatment.



### 5.2.12 Nausea and vomiting

A high level of calcium in the blood (hypercalcaemia), side-effects from chemotherapy drugs and 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 (anti-nausea medicine). 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.

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

### 5.2.13 Neutropenia (low level of neutrophils)

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 neutropenia.

Infection is harder to fight if you have myeloma and neutropenia, so watch out for signs such as 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.

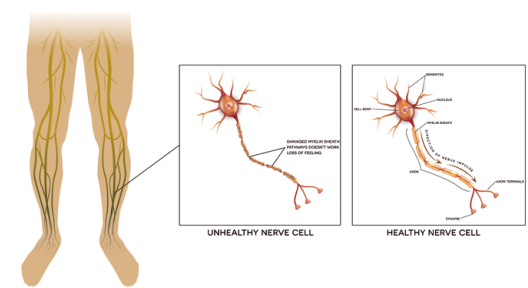
The risk is also increased because the lining of the gut can be damaged by chemotherapy and radiotherapy, which makes it easier for bacteria in food to enter the bloodstream.

If you develop neutropenia, 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 pâtés.

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 consider, 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 thus increasing the chance of contamination. Always store raw and cooked foods separately and make sure that any frozen food is covered and stored at the bottom of the fridge (rather than at room temperature) for defrosting, to avoid it dripping onto other food. Cook all food thoroughly until it is piping hot throughout and the meat juices run clear.

Take care with hand hygiene: always wash your 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.



### 5.2.14 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.

### 5.2.15 Peripheral neuropathy

Peripheral neuropathy means damage to the peripheral nervous system; 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). Some of the neuropathy caused by medications may subside once you stop or change doses, but some of it may also be permanent.

Pain from peripheral neuropathy can be relieved by a range of drugs, including amitriptyline, 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.

### **5.2.16 Skin conditions**

Thalidomide and bortezomib (Velcade) can result in dry, itchy skin rashes, or 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.

### **5.2.17 Spinal cord compression**

Myeloma bone disease involves the breakdown of bone faster 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 or genital area, and it may also involve incontinence, inability to pass urine, or constipation.

Urgent treatment is required, and this is considered an emergency. To prevent permanent damage to your spinal cord a surgical procedure may be needed. One option is a 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.

### **5.2.18 Thrombocytopenia (low level of blood platelets)**

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 thrombocytopenia, 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.

The routine lab test looking at your complete 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 thrombocytopenia is a side effect of treatment, it may be necessary to reduce the dose, or delay treatment until your platelet level recovers.

You should monitor 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 your

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.

### 5.2.19 Cytokine release syndrome (CRS) and neurotoxicity

Newer and emerging treatments such as chimeric antigen receptor (CAR-T) therapy and bispecific monoclonal antibodies have side effects not often seen with other treatments with myeloma. Cytokine release syndrome, also known as CRS, occurs when your immune cells (T cells) are active and release a substance called cytokines. CRS is a systemic inflammatory condition which appears as a flu-like illness and may include symptoms such as fever, fatigue, nausea, difficulty breathing and/or high heart rate. Neurotoxicity may appear as confusion, lethargy, headache, altered

mental state, difficulty speaking and, in rare but severe cases, seizures. Both can be dangerous and, if left untreated, can be fatal. In many cases these symptoms are managed in a hospital setting and sometimes in an intensive care unit.

## 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 have a good idea of what to expect.

For the doctors and nurses to provide the right treatment and ease any pain or discomfort you may be experiencing, you must tell them 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 from feeling tired and 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.

### 5.3.3 Physical activity and exercise

When you feel able to, take some gentle exercise, 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 your muscles, and also give a good feeling that you are looking after yourself. Walking, swimming and aqua fitness are all good choices, as are exercise regimes such as 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 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 when 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 antifungal or antiviral treatments. You should avoid foods that may increase the soreness, or are salty, spicy or acidic.

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 5.2.18), 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 check-up and any invasive dental treatment done first. Despite this very small risk, it is important for everyone with myeloma to be routinely 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 well enough to be 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 stronger sense 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 in something you never previously had enough time for. 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

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 differently, so it is impossible for doctors to tell you exactly how your body 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.

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

#### 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. 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 symptoms that can be worrisome and would mean that you should call for medical help.

While your active treatment is underway, it can be easy to feel that what you are going through is hard for you and your family to live with. Living with myeloma is much more of a challenge than simply enduring the symptoms and side effects of treatment, since it may interfere with some of your normal activities. You may feel a sense of loss of time and freedom. At times this may 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 these feelings are normal. Try to do things you enjoy, but don't feel guilty if some days are not so positive. 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 may feel better and able to gradually resume your normal life activities again. In some countries, and in some cases, maintenance treatment, e.g., a low dose of lenalidomide or thalidomide, is given over a long period, with the aim of making the period of remission last for 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 options may be beneficial, but may not necessarily be available in your country, nor recommended by your haematologist given your specific circumstances.

Your myeloma may become resistance to treatment, or you may not respond to treatment at all. This is known as refractory myeloma.

This can be 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. Continue to talk to family members, friends and health care professionals about how you are feeling. Stay informed about future treatments and the possible options for the future. It is OK to feel sad and upset. Tell your health care team who have experience supporting patients and family members in similar situations.

### 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 in Europe, but they are likely to be every few weeks/months and will be set by your physician. Because myeloma is a complicated condition have many questions, it is a good idea to think carefully about any questions that you have before your check-ups.

We recommend writing down any symptoms, feelings, or treatments you may have questions about and keep a diary in the days or weeks before to ensure you 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 next appointment. Many people find it helpful to take their partner or friend with them; this can enable 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

Continuing to work, if you can, may help you maintain a sense of normalcy. When you have been diagnosed with myeloma, you will need to contact your employer and come to an 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 written confirmation of your diagnosis, which will explain how it may affect your ability to work. Many employers are becoming more flexible about hours, especially with people who have health conditions, and it may be possible to investigate reducing your hours as well as your level of responsibility, if that would help.

If you look after someone else who is dependent on you, such as children or elderly parents, it is sensible to make some other arrangements for their care in the case of an emergency, or when you must go to appointments. You may not need to put the emergency 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 do not 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 or if 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 or near the time you plan to travel.

If you are travelling within the European Economic Area<sup>6</sup> or Switzerland, you can benefit from the same health care services as are available to residents of those countries for free, or at a reduced cost, 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.

<sup>6</sup>The European Economic Area consists of the 27 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, and Sweden; and the UK if you were in the EU before the end of 2020) PLUS Iceland, Liechtenstein and Norway.

Being treated for myeloma may mean that you need to take a significant amount of time off work or even permanent leave, 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 several 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, from your community/citizens advice bureau, 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 interventions or treatments you do or do not want. Some decisions are made when people are nearing the end of their life and they choose to have (or not have) artificial feeding tubes for nutrition, to be put on a ventilator or not, or if they would or would not want cardiopulmonary resuscitation (CPR). It is important, yet understandably difficult, to discuss these situations with your family, loved ones, or anyone who would be responsible for making decisions for you (if/when you are unable). These discussions should focus on your definition of quality of life and under what circumstances you would (or would not) want these measures.

It can also be helpful to discuss with a doctor what interventions or 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 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 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.

## 6.7 Palliative care

The World Health Organisation (WHO) defines palliative care as “an approach [to treatment] that improves the quality of life of patients and their families who are facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and correct assessment and treatment of pain and other problems, whether physical, psychosocial or spiritual.”

Palliative care is not just for the end of life – you may receive palliative care earlier in your illness, while you are still receiving other therapies to treat your condition. Palliative care is offered in various settings (at home or in hospital) and may look different depending on what country you live. If your symptoms are worsening, or you are experiencing other issues or concerns and need more support, speak with your treating doctor about your options for palliative care, or other supportive care options.

End of life care should help you to live as well as possible until you die. The people providing your care should ask you about your needs and preferences, and take these into account as they work with you to plan your care. They should also support your family, carers, or other people who are important to you. While difficult, it is never too early to discuss these matters with your loved ones.

## 7. Myeloma landscape and future directions

### 7.1 Approved treatments for myeloma

The development of anti-myeloma treatments over the last 10 years has greatly improved the prospects and quality of life for people with myeloma. Combinations of these treatments authorised for use in Europe and the indications are shown below:

- **belantamab mafodotin (Blenrep)** is approved alone (as a monotherapy) for the treatment of patients that have had at least four prior therapies (inclusive of a proteasome inhibitor, immunomodulatory agent, anti-CD38 monoclonal antibody) and continue to have worsening of their myeloma.
- **bortezomib (Velcade)** is approved alone or in combination with doxorubicin (a chemotherapy drug) or dexamethasone (a steroid) for patients that have received at least one prior therapy and are not eligible (or have previously had) a stem cell transplant.
- **carfilzomib (Kyprolis)** is approved in combination with dexamethasone with or without lenalidomide (Revlimid) for patients who have had at least one prior therapy.
- **daratumumab (Darzalex)** is approved in combination with lenalidomide and dexamethasone, or with bortezomib (Velcade), melphalan (a chemotherapy drug) and prednisone (a steroid) for the treatment of newly-diagnosed patients that are ineligible for stem cell transplant; it is also approved in combination with bortezomib (Velcade), thalidomide and dexamethasone for the treatment of newly-diagnosed patients that are eligible for transplant; is also approved in combination with lenalidomide and dexamethasone or bortezomib (Velcade) and dexamethasone for treatment of patients that have had at least one prior therapy; or it is approved alone (as a monotherapy) for relapsed refractory patients that have previously had a proteasome inhibitor, immunomodulatory agent and still have worsening disease.
- **elotuzumab (Empliciti)** is approved in combination with lenalidomide

(Revlimid) and dexamethasone in patients that have received 1-3 prior therapies. It is also approved in combination with pomalidomide (Imnovid) and dexamethasone for patients that have had at least two prior therapies, including lenalidomide (Revlimid), and a proteasome inhibitor and their disease has worsened on their last treatment.

- **idecabtagene vicleucel (Abecma)**: is a chimeric antigen receptor (CAR-T) cell therapy and is approved alone for patients that have relapsed or refractory disease and have previously been treated with at least three therapies an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody.
- **isatuximab (Sarclisa)** is approved in combination with pomalidomide (Imnovid) and dexamethasone for patients that have had at least two prior therapies (inclusive of lenalidomide [Revlimid] and a proteasome inhibitor) and their disease has worsened on their last treatment.
- **ixazomib (Ninlaro)** is approved in combination with lenalidomide (Revlimid) and dexamethasone for patients that have had at least one prior therapy.
- **lenalidomide (Revlimid)** is approved alone for maintenance treatment of patients with newly diagnosed myeloma that have just undergone stem cell transplant; also in combination with dexamethasone with or without bortezomib (Velcade), or melphalan and prednisone for newly-diagnosed patients that are ineligible for stem cell transplant; also in combination with dexamethasone for patients that have had at least one prior therapy
- **thalidomide** is approved in combination with melphalan and prednisone for newly diagnosed patients that are older than 65 and ineligible for stem cell transplant.
- **panobinostat (Farydak)** is approved in combination with bortezomib (Velcade) and dexamethasone, for patients that have had at least two prior therapies, including bortezomib and an immunomodulatory agent.
- **pomalidomide (Imnovid)** is approved in combination with bortezomib (Velcade) and dexamethasone for patients that have received at least one prior treatment regimen (inclusive of lenalidomide); it is also approved in combination with dexamethasone for patients that have had at least two prior treatment regimens (inclusive of lenalidomide [Revlimid] and bortezomib [Velcade]) and their disease continues to worsen.



- **selinexor (Nexpovio):** is used in combination with dexamethasone to treat patients that have had at least four previous treatments and their myeloma is no longer responding.

## 7.2 New targets and investigative drugs to treat myeloma

There continues to be significant research in the genetic changes causing myeloma and their influence on 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 been completely mapped by the Multiple Myeloma Genomics Initiative of the Multiple Myeloma Research Foundation. The concept of personalised medicine using genetic analysis will likely 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, fitness and specific disease characteristics.

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 the 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.

There are many therapies currently under investigation for the treatment of myeloma, many with promising results. While the above treatments have significantly improved survival, myeloma still remains an incurable illness. In patients who have exhausted all their previous treatment options they may be eligible to enrol in a clinical trial (section 7.3).

Some types of drugs under investigation for the treatment of myeloma are chimeric antigen receptor cell therapy (also known as CAR-T-cell therapy) and bispecific monoclonal antibodies. Both treatments harness the immune system to fight myeloma.

MPE has developed a series of factsheets covering the myeloma treatments mentioned above. Please, check the MPE factsheet section in the following link: [www.mpeurope.org/factsheets/](http://www.mpeurope.org/factsheets/)

### 7.2.1 CAR-T-cell therapy

CAR-T-cell therapy first removes, then genetically programmes, your body's T-cells (a type of immune cell). After the genetically programmed T-cells are reinfused into your body they can find and kill myeloma cells. This type of treatment has been shown to be very effective in myeloma, but this remains under investigation as response may not be long lasting.

You can find more information about CAR-T treatment in the MPE website. Check the educational resources section where you can find Q&As, factsheets, toolkits, webinars, and educational clips: [www.mpeurope.org/educational-resources/](http://www.mpeurope.org/educational-resources/)

### 7.2.2 Bispecific antibodies

Bispecific monoclonal antibodies are laboratory produced antibodies that bind to both myeloma cells and an immune cell to stimulate immune cells to kill myeloma cells. The preliminary results from these studies have also shown that they are effective.

While these emerging therapies are promising, they are not without significant and sometimes dangerous side effects. Therefore, before considering enrolment in a clinical trial you should make sure you are well informed. Next, we will talk about the details on what is involved and define the components of a clinical trial.

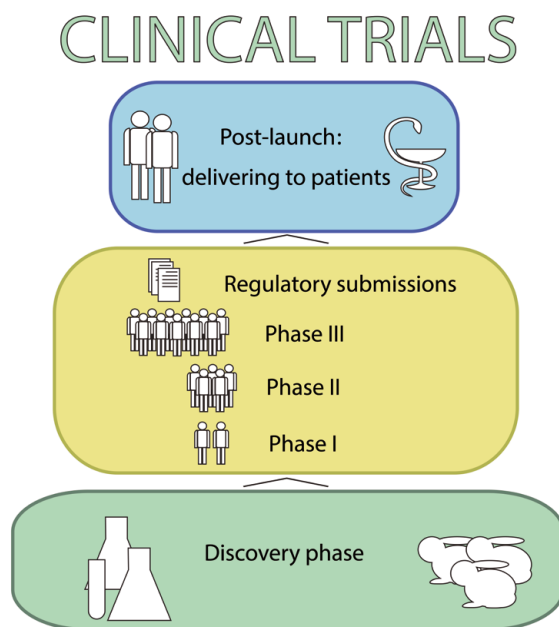
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## 7.3 What are clinical trials?

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 the people taking part.

Before a new medication can enter the market and become 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 and other health conditions etc. Many people with myeloma are keen to participate in trials because they give access to new treatments before they are widely available.

Clinical trials are usually carried out in hospitals and it often takes 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 a 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 several 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 regulation<sup>7</sup>, 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; this often leads to different interpretations in 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.

### 7.3.1 Clinical Trial 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 those unwanted effects.

Phase II trials will be conducted on products or treatments that have already successfully completed Phase I, and typically involve up to 300 patients. Larger numbers are needed to ensure 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 that are already in use, but are being tested in a new combination or approach, will start with Phase II.

For medications that 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 quality of life. All these parameters will be compared with the benefits gained from the 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 benefits from the new treatment compared to existing treatments, and if the side effects are

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

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 the participant or the doctor to misinterpret the results.

Phase IV of clinical trials occur after a drug has launched and is available on the market. This phase includes real-world studies and continued surveillance of efficacy and side effects of approved treatments.

### **7.3.2 Inclusion and exclusion criteria**

The protocol for every clinical trial defines its exact purpose, so the researchers must be sure that the participants meet clear criteria. This criterion is necessary so that the trial results represent only what is being tested and cannot 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.

In addition to criteria for inclusion there are specific criteria set by researchers that are likely to exclude potential participants for the study given safety or other concerns. This is again to ensure that the intended patient population is included in the study and therefore reflected properly in the results.

### **7.3.3 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.

## **7.4 Finding out about myeloma clinical trials**

Clinical trials currently underway in Europe are all listed on the European Clinical Trials Register, <https://www.clinicaltrialsregister.eu/> or those in Europe and the world can be found at [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

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 as these databases can be difficult for patients to navigate. Your doctor will also have access, or can find the 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.



## Acknowledgements

Myeloma Patients Europe would like to acknowledge the use of information from Myeloma UK and Bloodwise (formerly Leukaemia & Lymphoma Research).

### Appendix – Sources of information and support

MPE is a network of European myeloma patient organisations. It supports national patient organisations to improve treatment and access for patients in their countries, and helps inform and raise awareness on a European level through its educational programmes. Please note, this information does not replace the information provided by your doctor.

Find out about your local myeloma group at <https://www.mpeurope.org/our-members/>

# Myeloma

## A Patients' Guide

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MYELOMA PATIENTS EUROPE



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