National University Cancer Institute Singapore

Multiple Myeloma

Patient's Booklet

A guide for cancer patients and their families

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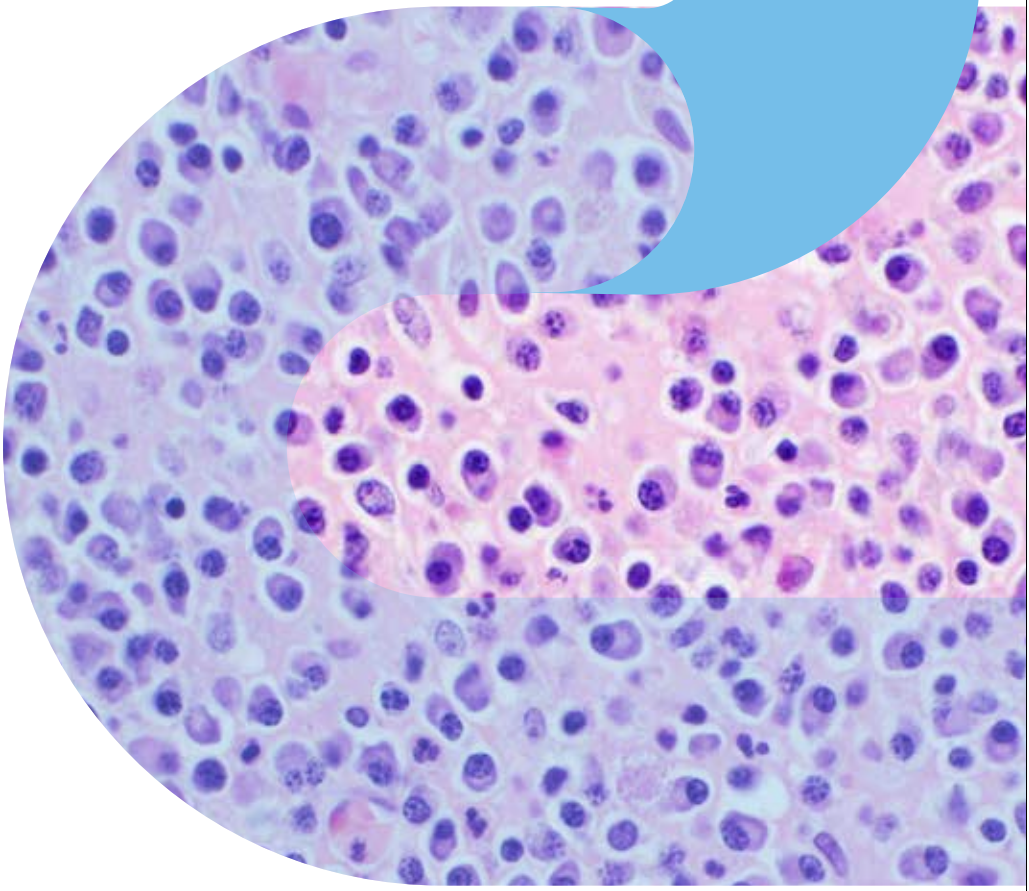
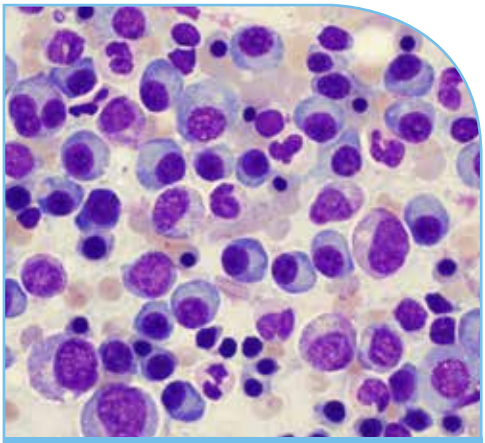


WHAT IS MULTIPLE MYELOMA?

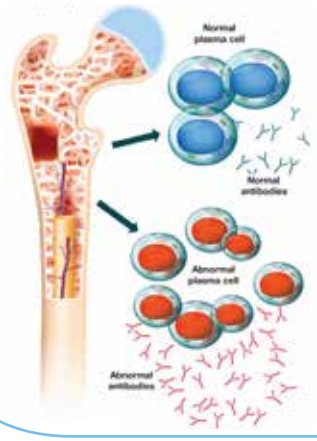
1. What is a plasma cell and what are plasma cell disorders?

A plasma cell is a type of cell derived from a specific type of white blood cells called B lymphocytes, which are primarily found in the bone marrow. These cells produce antibodies (also known as immunoglobulins, normally made up of two short light and two longer heavy joined protein chains), which fight against infections. Normally, when bacteria or viruses enter the body, the B lymphocytes are triggered to differentiate (transform) into plasma cells. The plasma cells then produce antibodies, which help to destroy the invading microorganisms. Normal plasma cells are short-lived and die after the body has been cleared of the infection.



Bone marrow plasma cells

Multiple myeloma



Plasma cell disorders are a result of certain chromosomal or genetic alterations that cause abnormal plasma cells, also called myeloma cells, to multiply uncontrollably and form tumours in the bones or soft tissues of the body. These abnormal plasma cells produce a specific class of "M protein" antibodies that are not needed by the body to fight infection. The abnormal plasma cells and antibody proteins can cause damage to the bone and kidneys, as well as reduce blood cell count and harm the immune system. Plasma cell disorders can be malignant (cancerous) or benign (not a cancer).

2. What is multiple myeloma?

Multiple myeloma, also known as "myeloma" or "plasma cell myeloma", is a blood cancer of the plasma cells of the bone marrow. In a healthy person, the role of plasma cells is to produce antibodies against infectious agents such as viruses and bacteria. Myeloma occurs when normal plasma cells become cancerous or malignant, and multiply uncontrollably.

Multiple myeloma causes plasma cells to:

- Accumulate in the bone marrow, weakening and damaging the bone. This can result in bone pain and fractures and can also lead to increased levels of calcium in the blood
- Produce abnormal antibodies (also known as monoclonal immunoglobulins or M proteins) that are not needed by the body to fight infection; these accumulate in organs such as the kidneys, restrict function and cause damage
- Overcrowd the bone marrow, outnumbering normal blood cells and limiting the production of healthy blood cells. Decreased blood cell numbers can cause anaemia, excessive bleeding and a decrease in the ability to fight infection

People with early stages of multiple myeloma may not have any symptoms at first, but the cancer can progress (see Figure 1).

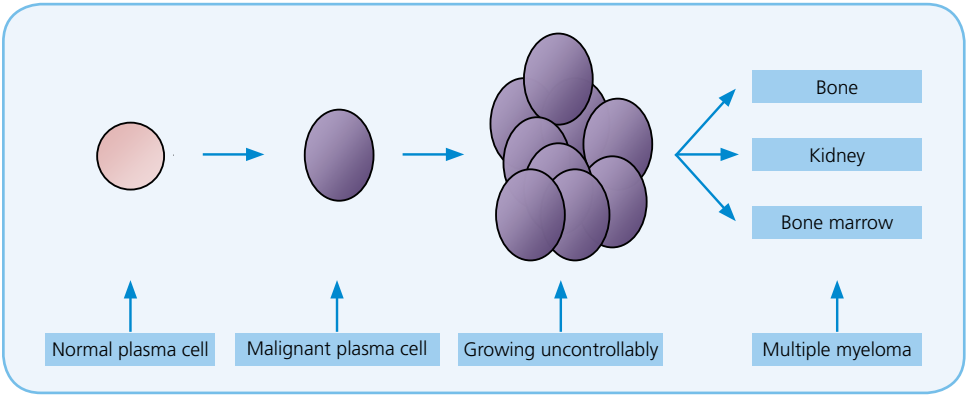


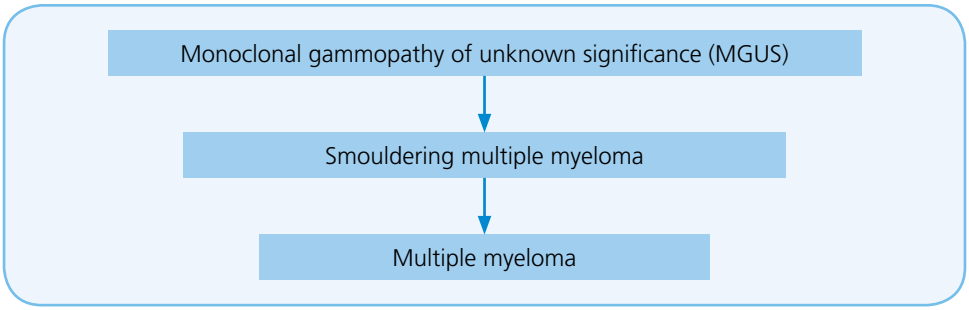
Figure 1

3. What are monoclonal gammopathy of undetermined significance (MGUS) and smouldering multiple myeloma (SMM)?

MGUS is a non-cancerous condition that resembles multiple myeloma in which plasma cells also produce abnormal antibodies. In MGUS, there is only a slight increase in plasma cells in the bone marrow; however, these plasma cells do not form an actual tumour or mass. They also do not usually cause symptoms like with multiple myeloma. Over time, a small number of people with MGUS will develop multiple myeloma.

SMM is a more advanced phase of MGUS or an early phase of multiple myeloma. Patients with SMM have a higher level of plasma cells in their bone marrow producing abnormal antibodies, but again, this does not usually cause symptoms.

MGUS and SMM are not cancerous but are sometimes considered as "premalignant" as they can eventually develop into a cancer. Patients diagnosed with MGUS or SMM do not usually require any treatment apart from regular follow-up by their doctor to see if the disease progresses.



4. What is a plasmacytoma?

A plasmacytoma is a single clump of cancerous plasma cells that has grown, forming an isolated tumour. A solitary plasmacytoma often develops within the bone, but it can also grow within soft tissues (such as the lungs or other organs). A plasmacytoma of the bone often develops into multiple myeloma, so patients are closely watched for signs of progression. It is not uncommon to feel pain where the plasmacytoma has developed. Radiation therapy, surgery, and chemotherapy are possible treatment options, depending on various factors – your doctor should discuss these with you.

5. What is amyloidosis?

Amyloidosis is also a disorder of plasma cell growth but with lower levels of abnormal plasma cells in the bone marrow as compared to multiple myeloma. The condition is caused by an abnormal protein called "amyloid" that becomes insoluble. Antibodies made by plasma cells are normally made up of joined protein chains (two short light chains and two longer heavy chains) [See Figure 2]. When affected by the disorder, the light chains of antibodies are distorted and produced in excess in a condition called "light-chain amyloidosis". These amyloid proteins build up in tissues, nerves or organs (such as the heart or kidney), disrupting their healthy functions as they become stiff, enlarged and unable to work. Amyloidosis can also be caused by a genetic disease or chronic infection.

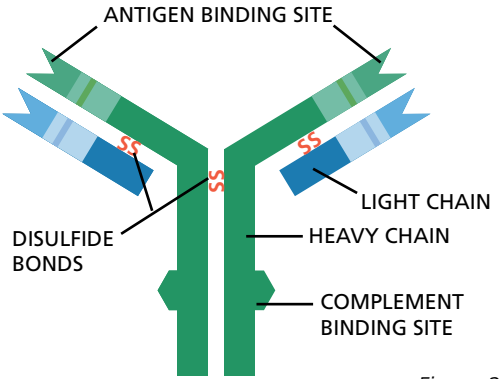


Figure 2

6. Why do I have multiple myeloma?

Although we have made advances in understanding how multiple myeloma develops, the exact cause has not yet been identified. Genetic mutations in the DNA of plasma cells can cause these cells to become abnormal and multiply rapidly. There are some specific mutations that have been identified as genetic risk factors, but these vary from patient to patient. That said, multiple myeloma is not thought to be a hereditary disease that can be passed from one generation to another.

Other factors can increase the risk of developing multiple myeloma; however, having a risk factor does not mean that a person will develop the disease. The risk of developing multiple myeloma increases with age, male gender, family history, obesity, and having other plasma cell disorders. Multiple myeloma is also more common in people of African descent. Exposure to toxic chemicals or atomic radiation and infection with cancer-related viruses have also been implicated as causes or triggers of multiple myeloma.

7. Is multiple myeloma curable?

While there is no known cure for multiple myeloma at present, it is a treatable disease and can be managed successfully for years in many patients using treatments such as a stem cell transplant or drug therapy. Treatment outcomes are continuously improving, and advancements in care have greatly improved survival rates and quality of life for most patients.

Please refer to section 3 for more information regarding treatment of multiple myeloma.

8. How long can a patient with multiple myeloma live?

Understanding your life expectancy after being diagnosed with multiple myeloma can help you and your doctor plan and decide on the best treatment and supportive care.

The overall 5-year relative survival rate is an estimate of the percentage of multiple myeloma patients expected to live at least 5 years after the cancer is found, excluding the risk of dying from other causes. Based on data from 2011 to 2017, 55.6% of patients are expected to survive 5 years or longer*.

The survival rate is also dependent on how advanced the cancer is at the time of diagnosis*:

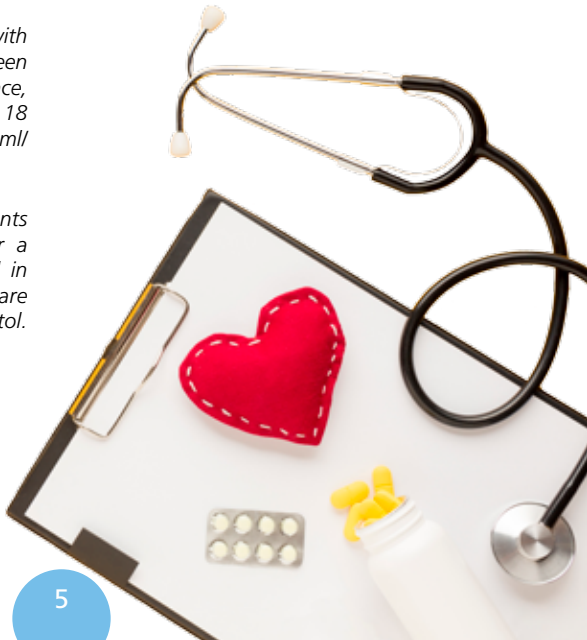
- For the 4% of patients who are diagnosed with multiple myeloma at an early stage, whereby the cancer is located at one site in the body, the 5-year survival rate is 77.5%
- If found at a later stage, the 5-year survival rate is reduced to 55.4%

The incidence and survival rate of multiple myeloma is known to vary by ethnicity. One analysis from 2014 reported that Asian countries have a relatively low incidence of multiple myeloma compared with Western countries, although this rate is increasing. This analysis found a median overall survival of 47 months (3.9 years); however, the age of the patient can heavily influence this†. Multiple myeloma patients under the age of 65 had a median overall survival of 55 months (4.6 years), compared with patients over the age of 65 surviving for 37 months (3.1 years).

Many other factors can affect survival, such as kidney function and overall health. It is important to remember that these survival rates are only estimates, as each patient is different and will react to therapy differently. Treatments are constantly evolving and improving, and these numbers are based on people who were diagnosed and treated at least 5 years ago.

**Numbers are based on people diagnosed with plasmacytomas or multiple myeloma between 2011 and 2017 from the US Surveillance, Epidemiology, and End Results (SEER) 18 database; https://seer.cancer.gov/statfacts/html/mulmy.html.*

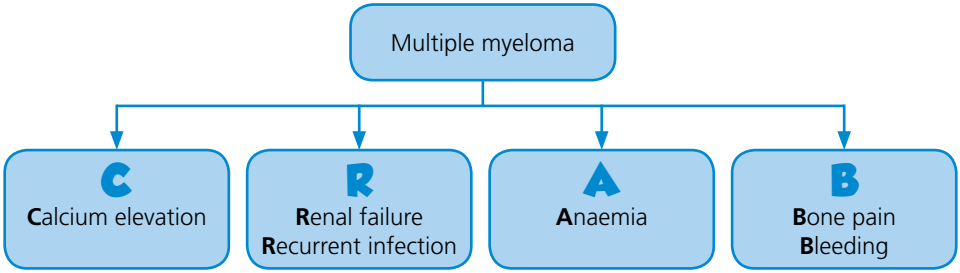
†Median survival refers to how long patients survive with a disease in general or after a certain treatment. It is the time (expressed in months or years) at which half of patients are expected to be alive; Kim K, et al. Am J Hematol. 2014;89:751–756.



9. What are the signs and symptoms of multiple myeloma?

The signs and symptoms of multiple myeloma vary from one individual to another. During the early stages of the disease (MGUS or SMM), there are often no symptoms, and the disease is usually discovered through routine blood tests. As the disease progresses, common symptoms include:

- Bone damage: Multiple myeloma causes bones to weaken, leading to bone pain and increased risk of bone fractures. The most commonly affected areas are the spine, pelvis and rib cage.
- Hypercalcaemia: Bone destruction can release excess calcium into the bloodstream, which may result in loss of appetite, muscle weakness, restlessness, increased thirst, increased urination, mental confusion, tiredness, abdominal pain, nausea and vomiting.
- Kidney problems: Excess M protein and calcium will overwork the kidneys as they filter the blood, resulting in damage or failure. This may impair the body's ability to remove excess salt, fluid, and waste, resulting in the swelling of the lower limbs and weakness.
- Anaemia: The growing number of cancerous plasma cells in the bone marrow can interfere with healthy red blood cell production, resulting in anaemia. Some myeloma treatments can also cause anaemia. Symptoms include fatigue, weakness, dizziness and shortness of breath.
- Recurrent infection: Cancerous plasma cells produce abnormal antibodies that are ineffective against infectious viruses or bacteria. These plasma cells also overcrowd and impair normal cells in the bone marrow, decreasing the production of healthy white blood cells and functional antibodies (a condition known as leukopenia). As a result, myeloma patients are more prone to infections and take a longer time to recover. Low white blood cell count can also occur as a side effect of chemotherapy.
- Increased bleeding: As the abnormal plasma cells multiply and overcrowd the normal cells in the bone marrow, the production of platelets is decreased (thrombocytopenia). This can lead to blood clotting issues such as frequent bleeding, nosebleeds, bleeding in the mouth and prolonged bleeding from cuts or scrapes. Low platelet count can also occur as a side effect of some drug treatments.



CRAB is the acronym for the most common symptoms of multiple myeloma

10. Why do I have bone pain?

Bone pain is a prominent clinical symptom of multiple myeloma. The cancerous plasma cells gather to form masses inside the bone marrow, which can disrupt the structure of the bone and may compress nerves, causing pain.

Cancerous multiple myeloma cells also secrete substances that trigger other cells in the bone marrow to attack and dissolve the bone (see Figure 3), while at the same time inhibiting the production of new bone. This causes soft spots known as osteolytic lesions, or bone weakening known as osteoporosis, which increases the risk of bone fractures. The most commonly affected areas are the spine, pelvis and rib cage.

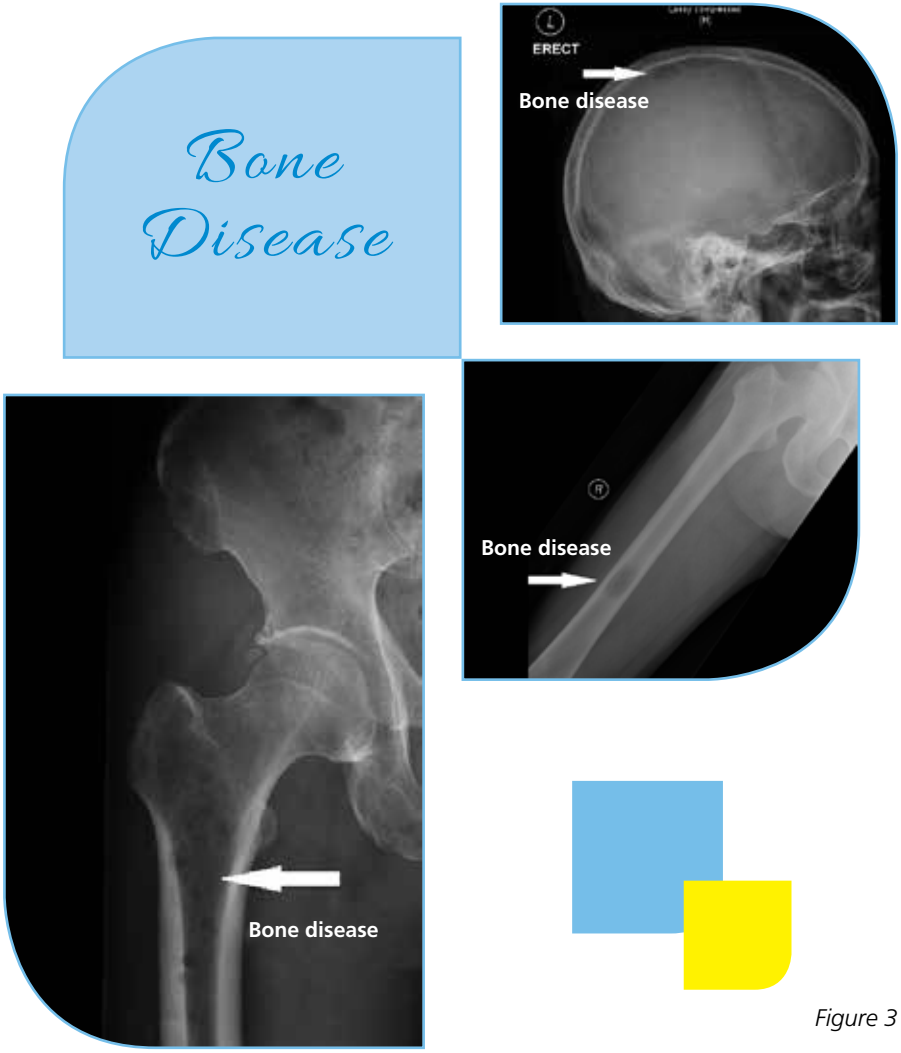


Figure 3

11. Why do I have a high calcium level?

As cancerous plasma cells attack the skeleton, the breakdown of bones releases calcium into the bloodstream. This results in an abnormally high level of calcium in your blood, a situation known as hypercalcaemia. Symptoms include loss of appetite, muscle weakness, restlessness, increased thirst, increased urination, mental confusion, tiredness, abdominal pain, nausea and vomiting. Severe hypercalcaemia can lead to kidney complications, coma or cardiac arrest, so it is important to identify and treat it quickly. Apart from bisphosphonates, your doctor may also prescribe you fluid hydration.

12. Why do I need to undergo dialysis?

Many multiple myeloma patients experience decreased kidney function over the course of their illness, and some develop progressive kidney failure. The production of M proteins by cancerous plasma cells can obstruct the kidney tubules and hinder their ability to filter the blood. Additionally, excess calcium in the blood can cause crystals to form and damage the kidneys. This will impair the body's ability to remove excess salt, fluid and waste, resulting in the swelling of the lower limbs and weakness.

If your doctor suspects impaired kidney function, they will perform blood tests to detect certain proteins. For patients who develop kidney failure, dialysis is an effective way of clearing unwanted waste, salt and water from their bodies.

13. What is anaemia?

Healthy bone marrow is involved in the production of red blood cells. When multiple myeloma affects the bone marrow, the growing number of cancerous cells can decrease the production of red blood cells, commonly resulting in a complication known as anaemia. Certain myeloma treatments such as chemotherapy can also cause anaemia.

Anaemia can cause symptoms such as weakness, fatigue, shortness of breath and dizziness. There are several supportive therapies available for treating anaemia in people with multiple myeloma. If the anaemia is severe, blood transfusions may be needed.

14. Why do I get infections easily?

In a healthy person, there are many plasma cells producing different types of antibodies to protect from a wide range of bacteria and viruses that can potentially cause infections. However, in a patient with multiple myeloma, the antibodies produced by cancerous plasma cells are ineffective at fighting infections. In addition, these abnormal plasma cells overcrowd and impair normal cells in the bone marrow, decreasing the production of healthy white blood cells and functional antibodies (a condition called leukopenia). On top of that, if a patient is receiving chemotherapy, the production of white blood cells in the bone marrow can be further reduced. As a result, multiple myeloma patients have a limited range of functioning antibodies and become more prone to frequent infection.

Tell your doctor right away if you experience symptoms such as fever, chills or sweating, muscle aches, coughing, sore throat, pain or redness at the site of an open wound, fatigue and diarrhoea. Preventative steps can be taken to reduce the risk of infection, such as washing hands frequently, avoiding contact with people who show signs of illness and keeping up to date with vaccines. Patients can take extra precautions to avoid cuts or scrapes, as well as wash fruits and vegetables and cook food thoroughly before eating.

15. Why am I at increased risk of bleeding?

In multiple myeloma, the abnormal plasma cells multiply and overcrowd the normal cells in the bone marrow, decreasing the production of regular blood cells and other elements, including platelets (a condition called thrombocytopenia). Normally, platelets stop the bleeding when a blood vessel is cut or damaged. These platelets clump together along with other blood elements to form a "clot", like a plug, to close the hole in the blood vessel.

A reduction in blood platelets can lead to blood clotting issues such as frequent bleeding, nosebleeds, bleeding in the mouth, and prolonged bleeding from cuts or scrapes. Low platelet count can also occur as a side effect of some antimyeloma drug treatments. Severe symptoms may require a platelet transfusion.

Abbreviations

MGUS Monoclonal gammopathy of undetermined significance
SMM Smouldering multiple myeloma

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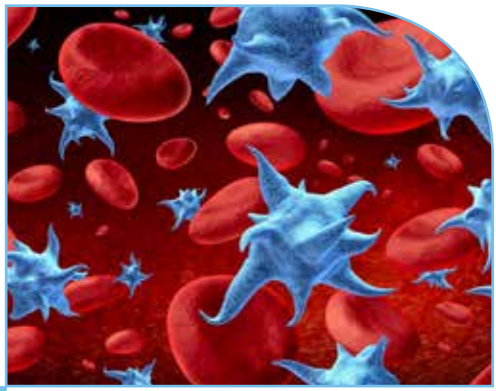

Diagnosis

16. Which tests should I be going for if my doctor suspects that I have multiple myeloma?

If your doctor suspects that you have multiple myeloma, they will usually perform a series of tests to confirm the initial diagnosis, assess the status of the disease and plan treatment.

Tests for multiple myeloma patients fall into three main categories: blood and urine tests, imaging studies and bone marrow tests. Each test can help your doctor gain more information about your diagnosis, enabling them to make tailored decisions. Your doctor may not ask you to do all of these tests, but some common multiple myeloma tests include:

Blood and urine tests:	
Complete blood count	This test measures levels of red blood cells, white blood cells, and platelets in the blood. If there are many cancerous myeloma cells in the bone marrow, some blood cell levels can be low
Blood chemistry and organ function tests	These blood tests check the proteins and other substances in your blood: ◆ Creatinine • High levels indicate that the kidneys are not functioning well ◆ Calcium • Increased bone breakdown can increase the levels of calcium, causing fatigue, weakness and confusion. It can also cause kidney damage ◆ Total blood protein testing measures albumin and globulin • Low albumin levels are more common in aggressive myeloma • The abnormal myeloma plasma cell "M protein" is a type of globulin. If total protein is elevated at diagnosis, your doctor may perform additional tests ◆ Lactate dehydrogenase • High levels can indicate worsened prognosis

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	◆ Serum ß2 microglobulin • High levels indicate more active and aggressive myeloma ◆ C-reactive protein • Increased C-reactive protein produced in the liver can signal active myeloma
Serum and urine protein electrophoresis (SPEP and UPEP)	The SPEP test is very important as it allows separation of all the proteins in the blood according to electrical charge to measure the amount of heavy-chain M protein made by myeloma cells. To a lesser extent, UPEP is also sometimes carried out to separate proteins in urine
Immunofixation electrophoresis (IFE) of blood or urine	Blood IFE also separates proteins by electrical charge, this time to indicate the type of M protein in the blood (i.e. heavy chain [G, A, D, or E] or light chain [kappa or lambda]). Again, this is carried out less often in urine
Quantitative immunoglobulin (QIg) testing	This is usually done as part of early myeloma screening to measure the level of immunoglobulin proteins in the blood
Serum free light chain (sFLC) assay	The sFLC test calculates the free light chain (FLC) ratio, which is used to see if there is more of one type of light chain (kappa or lambda) than the other, which can be a sign of myeloma
Routine urinalysis	This test finds the presence of protein in urine, which can be indicative of impaired kidney function
Imaging studies:	
X-ray	X-rays can be used to identify loss or thinning of bone, holes in bone or fractures
Magnetic resonance imaging (MRI)	MRI scans can rapidly detect early lesions in patients with smouldering multiple myeloma, plasmacytomas and spinal cord compression
Computed tomography (CT)	This type of scan uses X-ray technology to create a 3D image of the body and can provide clear images of bone lesions
Positron emission tomography (PET)	PET scans require injection with a certain compound that is taken up by actively growing cancer cells in the body. These scans are useful when blood or urine tests do not provide enough information, or if a patient has nonsecretory myeloma

Bone marrow tests:	
Bone marrow aspiration and core biopsy	As myeloma grows inside the bone marrow, these tests provide direct access to collect potential tumour cells. Cells will be examined under a microscope for abnormalities and may undergo various other tests, such as immunophenotyping, cytogenetic studies, fluorescence in situ hybridisation or gene expression profiling
Other tissue biopsies	Fine needle aspiration or core needle aspiration may be used to sample other tissues, such as lymph nodes or tumours, to examine the cells

Before undergoing any tests, consult with your doctor to make sure that there are no special instructions about taking certain medications, supplements, food or drinks. After the tests, discuss the results with your doctor to learn what they mean for you.

17. What are the diagnostic criteria for plasma cell disorders?

International criteria for the diagnosis of multiple myeloma have been established. Updated criteria also allow for diagnosis of patients with plasma cell disorders who are at high risk of progression to symptomatic disease so that they can benefit from early treatment.

Plasma cell disorder	Diagnostic criteria
Active multiple myeloma	Monoclonal bone marrow plasma cells > 10% or biopsy-proven bony or extramedullary plasmacytoma, and any one or more of the following myeloma-defining events: 1. Any one or more of the following CRAB features indicating end-organ damage attributable to an underlying plasma cell proliferative disorder: ◆ Hypercalcaemia: Serum calcium > 0.25 mmol/L (> 1 mg/dL) higher than the upper limit of normal, or > 2.75 mmol/L (> 11 mg/dL) ◆ Renal insufficiency: Creatinine clearance < 40 mL/min or serum creatinine > 177 µmol/L (> 2 mg/dL) ◆ Anaemia: Haemoglobin > 20 g/L below the lowest limit of normal, or < 100 g/L ◆ Bone lesions: ≥ 1 osteolytic lesion on skeletal radiography, CT, or PET/CT. If bone marrow has < 10% clonal plasma cells, ≥ 1 bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement

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	2. Any one or more of the following biomarkers of malignancy: ◆ Clonal plasma cells ≥ 60% upon bone marrow examination ◆ Serum involved/uninvolved FLC ratio ≥ 100, provided the absolute level of the involved light chain is at least 100 mg/L ◆ > 1 focal lesion on MRI that is at least 5 mm or greater in size
Smouldering multiple myeloma (SMM)	Both criteria must be met: ◆ Serum monoclonal protein (IgG or IgA) ≥ 30 g/L or urinary monoclonal protein ≥ 500 mg/24h, and/or clonal bone marrow plasma cells 10–60% ◆ Absence of myeloma-defining events or amyloidosis
Non-IgM monoclonal gammopathy of undetermined significance (MGUS)	◆ Serum monoclonal protein < 30 g/L ◆ Clonal bone marrow plasma cells < 10% ◆ Absence of end-organ damage such as CRAB symptoms or amyloidosis that can be attributed to the plasma cell proliferative disorder
IgM MGUS	◆ Serum IgM monoclonal protein < 30 g/L ◆ Bone marrow lymphoplasmacytic infiltration < 10% ◆ No evidence of anaemia, constitutional symptoms, hyperviscosity, lymphadenopathy, hepatosplenomegaly, or other end-organ damage that can be attributed to the plasma cell proliferative disorder
Light-chain MGUS	◆ Abnormal FLC ratio (< 0.26 or > 1.65) ◆ Increased level of the appropriate FLC (increased kappa FLC in patients with ratio > 1.65 and increased lambda FLC in patients with ratio < 0.26) ◆ No immunoglobulin heavy-chain expression on immunofixation ◆ Absence of end-organ damage such as CRAB symptoms or amyloidosis that can be attributed to the plasma cell proliferative disorder ◆ Clonal bone marrow plasma cells < 10% ◆ Urinary monoclonal protein < 500 mg/24h

Solitary plasmacytoma	◆ Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells ◆ Normal bone marrow with no evidence of clonal plasma cells ◆ Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) ◆ Absence of end-organ damage such as CRAB symptoms or amyloidosis that can be attributed to the plasma cell proliferative disorder

18. What is a bone marrow examination and what are the side effects?

Bone marrow is the spongelike, flexible tissue found inside the body's larger bones, comprising a fluid portion and a more solid portion containing blood cells and plasma cells. As multiple myeloma grows inside the bone marrow, a bone marrow examination consisting of two parts may be needed to collect and examine cells:

- Bone marrow aspiration – a needle is used to withdraw a sample of the fluid portion of the bone marrow
- Bone marrow biopsy – a needle is used to withdraw a small sample of the solid bone marrow

In both procedures, the bone marrow sample usually comes from the pelvic bone, in your lower back near your hip. Doctors often do these two procedures at the same time, referred to together as a bone marrow examination. However, your doctor will decide whether you need one or both procedures. Bone marrow examinations may be done in outpatient clinics or hospital wards. Informed consent for this procedure is required.

How to prepare

Your doctor will tell you whether you can eat or drink normally before the test. Inform your doctor about medications and supplements you take, especially if these increase your risk of bleeding.

What to expect

You will be asked to lie on your abdomen or on your side. After the skin is cleansed with antiseptic, a local anaesthetic will be injected to numb the area where the biopsy needles will be inserted. You may also be pretreated with sedation, painkillers, and/or anti-anxiety medications, although this is not routine practice.

Typically, bone marrow aspiration is performed first. A hollow aspirate needle is inserted through the skin, then through the bone into the bone marrow (see Figure 4). Once the needle is in the cavity, a syringe will be attached to the needle to withdraw a sample of the liquid bone marrow. Several samples may be taken. There is usually some discomfort or a brief sharp pain when fluid is aspirated from the bone marrow, but this procedure will be over within a few minutes. Rarely, when fluid cannot be withdrawn, the needle is moved for another attempt.

Subsequently, a biopsy will be performed if required. In a biopsy, a larger needle will be advanced further inwards and rotated to obtain a solid cylindrical piece of bone marrow about 1 cm long. This bone marrow is then removed, along with the needle. The entire procedure, factoring in preparation time, typically takes about 30–45 minutes.

After the procedure

A bandage will be placed over the site to prevent bleeding. You will be asked to lie on your back for some time and apply pressure to the procedure site. Thereafter, assuming that no bleeding is observed, you can then get up and go about your normal activities. If you have received sedation, you will be taken to a recovery area.

Paracetamol or other painkillers can be used to ease soreness, which is common 2–3 days post procedure. Any worsening pain, redness, fever, bleeding or swelling may suggest a complication. You should also avoid washing the procedure site for at least 24 hours to keep it clean and dry.

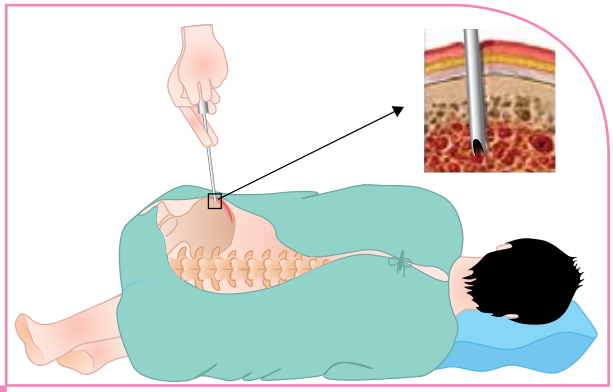

Figure 4

19. What information can a bone marrow test provide?

A bone marrow examination (aspirate and/or biopsy) can confirm diagnosis of multiple myeloma and provide information on the status of the disease. It is also through this procedure that samples required for cytogenetic and fluorescence in situ hybridisation tests can be obtained, to investigate any molecular or genetic abnormalities that can help to predict disease course. Bone marrow tests are also used for monitoring over the course of treatment.

20. What is a skeletal survey and what are the side effects?

A skeletal survey is a series of bone X-rays done on different areas of your body, including the skull, vertebral column, rib cage, limbs, and pelvic bone. They are usually used to identify focal or widespread abnormalities of the skeleton caused by multiple myeloma.

During the procedure, you will be positioned by a radiology technologist, who will ask you to stay still and perhaps hold your breath for a few seconds. A typical skeletal survey consists of around 20 individual X-rays and takes approximately 30 minutes. These are usually performed on an outpatient basis at an imaging centre in the hospital.

Any imaging study that uses X-rays involves ionising radiation. Overall, there is a low risk of adverse health effects related to radiation exposure from one skeletal survey. In reality, we are exposed to natural radiation in our surroundings every day. Should your doctor request you to undergo a skeletal survey, they will be confident that the benefits of the test far outweigh any risks. That being said, the risks of radiation are slightly higher when it comes to unborn children, so female patients aged 10–55 years will be asked if they have had regular menstrual cycles prior to the test to rule out any chance of pregnancy.

21. How do I read my test results?

You can ask your physician for a copy of your test results. Normal laboratory values (usually expressed as a range of values in parentheses next to your laboratory results) vary. Note the type of units used (eg, grams or milligrams, litres or decilitres) and ensure that you only compare results expressed in the same units.

If your laboratory result is above the upper limit or below the lower limit of the normal range, your reported laboratory value will be assigned a symbol denoting that it is out of range (usually H=high or L=low). You should discuss the significance of any abnormal laboratory value with your physician. In general, a trend or pattern observed from a series of test results gathered over time often reveals more information about your condition than looking at results from just one particular test.

22. Do patients with seemingly similar presentation and diagnosis share the same prognosis?

Prognosis is a prediction of how your multiple myeloma outlook will change over time. Several prognostic indicators can help determine how fast the cancer is growing, the extent of disease, genetic abnormalities, response to therapy, and overall health status. The following are some of the significant factors contributing to your multiple myeloma prognosis:

- Age: Older patients with this condition are usually frail, with weakness, low physical activity and a higher risk of adverse events. They are more likely to have a poorer prognosis than younger patients
- Stage of disease: Patients who have a lower stage of multiple myeloma usually have a better prognosis
- Symptoms: Severe symptoms of multiple myeloma, especially kidney failure measured by the creatinine level in the blood, can lead to a lower chance of survival. However, supportive therapy such as dialysis can help improve kidney function in people with multiple myeloma
- Laboratory findings: Abnormal clinical and laboratory test findings (eg, albumin, lactate dehydrogenase, creatinine, ß2 microglobulin) are considered prognostic indicators that can help determine changes in disease activity
- Chromosome changes: Doctors look at plasma cells from the bone marrow to see if there are changes to the chromosomes. Some changes are linked to poorer prognosis because people with these abnormalities only benefit from specific forms of treatment. Changes include:
    - A missing chromosome 13 (called a deletion)
    - Missing part of chromosome 17 (called a 17p deletion)
    - A rearranged chromosome 14 (called a translocation)
    - An extra copy of part of chromosome 1 (called a gain or amplification)

- Gene expression: Researchers have found genes that have highly elevated expression (e.g. FGFR3 and CCND1) in patients with multiple myeloma. Some genes are linked to better response to treatment and improved prognosis

- Treatment response: Patients whose cancer responds well to treatment and goes into complete remission have a better prognosis than patients whose cancer does not respond to the initial treatment

23. What is the International Staging System (ISS)?

The stage of multiple myeloma refers to the degree to which the cancer has progressed. Determining the stage of disease is one of the most significant factors in identifying the severity of the disease in order to develop a personalised treatment plan.

One of the most commonly used staging systems for multiple myeloma is the International Staging System (ISS). It is primarily based on two blood test results, serum ß2 microglobulin (ß2M) and albumin, to provide a simple three-stage classification with clear outcomes. ß2M is a protein that indicates the extent of myeloma disease, while albumin is an indicator of overall general health.

ISS stage	Criteria
I	Serum ß2M < 3.5 mg/L AND serum albumin ≥ 3.5 g/dL
II	Serum ß2M < 3.5 mg/L AND serum albumin < 3.5 g/dL OR Serum ß2M 3.5–5.5 mg/L irrespective of serum albumin
III	Serum ß2M ≥ 5.5 mg/L

24. What is the Revised International Staging System (R-ISS)?

The ISS was later revised to include two more validated and reliable prognostic factors for multiple myeloma – genetic risk as assessed by interphase fluorescence in situ hybridisation (iFISH) and level of lactate dehydrogenase (LDH) – in addition to serum ß2M and albumin. It can identify high-risk patients because of the additional parameters.

R-ISS stage	Criteria
I	ISS stage I (serum ß2M < 3.5 mg/L AND serum albumin ≥ 3.5 g/dL) AND Standard-risk chromosomal abnormalities by iFISH AND Normal LDH
II	Not R-ISS stage I or III
III	ISS stage III (serum ß2M ≥ 5.5 mg/L) AND either High-risk chromosomal abnormalities by iFISH OR High LDH

25. How do we differentiate multiple myeloma from other diseases?

Multiple myeloma shares many signs and symptoms with other benign and malignant diseases, such as metastatic bone disease from a different cancer, Waldenström macroglobulinaemia (a lymphoma), kidney disease and so on. It is important to distinguish multiple myeloma from benign causes that have the same findings, and from other plasma cell malignancies, in order to identify the prognosis and treatment plan. The tests mentioned in this section could help your physician confirm your diagnosis.

Abbreviations

ß2M Serum ß2 microglobulin
CRAB Calcium elevation, renal failure, recurrent infection, anaemia, bone pain, and bleeding
CT Computed tomography
FLC Free light chain
IFE Immunofixation electrophoresis
iFISH Interphase fluorescence in situ hybridisation
ISS International Staging System
LDH Lactate dehydrogenase
MGUS Monoclonal gammopathy of undetermined significance
MRI Magnetic resonance imaging
PET Positron emission tomography
QIg Quantitative immunoglobulin
R-ISS Revised International Staging System
sFLC Serum free light chain
SMM Smouldering multiple myeloma
SPEP Serum protein electrophoresis
UPEP Urine protein electrophoresis

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Treatment

TREATMENT

26. How many treatment options do I have?

Nowadays, patients with multiple myeloma have many treatment options. Patients with active, symptomatic multiple myeloma or asymptomatic smouldering multiple myeloma (SMM) with one or more myeloma-defining events (MDEs) will most likely need to begin treatment. The main types of drug therapies used to treat multiple myeloma as single agents or in combination are:

- Proteasome inhibitors (bortezomib [Velcade], carfilzomib [Kyprolis], ixazomib [Ninlaro])
- Immunomodulatory drugs (lenalidomide [Revlimid], thalidomide [Thalomid], pomalidomide [Pomalyst])
- Steroids (dexamethasone [Decadron], prednisone [Deltasone])
- Histone deacetylase inhibitors (panobinostat [Farydak])
- Monoclonal antibodies (daratumumab [Darzalex], elotuzumab [Empliciti])
- Chemotherapy agents (melphalan [Alkeran/Evomela/Alphalan], cyclophosphamide [Cytoxan])

Induction therapy aims to effectively control and destroy multiple myeloma cells while reversing myeloma-related complications. Although a single drug may be used to treat multiple myeloma initially, it is useful in some patients to use combinations of different types of drugs to target the cancer from multiple pathways. The combination of drugs will depend on the patient's overall risk, disease characteristics such as stage and genetics, and whether the patient is eligible for stem cell transplantation.

Typical induction combinations of therapy include:

Transplant eligible:

- Bortezomib + thalidomide + dexamethasone
- Bortezomib + cyclophosphamide + dexamethasone
- Bortezomib + lenalidomide + low-dose dexamethasone
- Daratumumab + bortezomib + thalidomide + dexamethasone
- Daratumumab + bortezomib + lenalidomide + low-dose dexamethasone

Transplant ineligible:

- Lenalidomide + dexamethasone
- Daratumumab + lenalidomide + dexamethasone
- Bortezomib + lenalidomide + low-dose dexamethasone

- Bortezomib + melphalan + prednisone
- Daratumumab + bortezomib + melphalan + prednisone
- Bortezomib + cyclophosphamide + dexamethasone

After induction therapy, patients eligible for a stem cell transplant will undergo the procedure. These patients will then receive consolidation therapy, which usually uses the same regimen as induction therapy to consolidate the gains made with the initial treatment cycles. For patients ineligible for transplant, induction therapy is used without consolidation therapy to gain treatment response. Low-dose maintenance therapy is then needed to maintain remission.

Typical combinations of maintenance therapy (transplant eligible and ineligible) include:

- Lenalidomide
- Thalidomide
- Bortezomib
- Ixazomib
- Daratumumab

Some patients may find clinical trials of emerging therapies to be a good option. Treatment options are also available should the cancer become active again at relapse.

27. What are the costs of the various treatment options?

The cost of each treatment option depends on a multitude of factors and may differ between institutions. You may be referred to a medical social worker to learn more about the financial assistance options available to you.

HEALTH 28. What is bortezomib?

Bortezomib (Velcade) was the first approved cancer therapy in a class of drugs known as proteasome inhibitors. By blocking the activity of proteasomes (components in the cell that remove unwanted protein), bortezomib targets and disrupts processes related to the growth and survival of cancer cells. Multiple myeloma cells stop dividing and producing chemicals that stimulate other cancer cells.

Bortezomib is commonly used as induction therapy in patients in combination with other anti-myeloma drugs as part of a multidrug regimen. Additionally, it can be used as maintenance and in cases of relapsed or refractory multiple myeloma.

Bortezomib is usually given by subcutaneous (SC; under the skin, usually in the thigh or abdomen) injection; it is rarely given by intravenous (IV; into the bloodstream) infusion. Varying treatment schedules may be used for patients receiving treatment for the first time, those receiving treatment for relapsed disease, and those receiving bortezomib in combination with other drugs. The length of treatment also varies according to the patient's response and whether the side effects are tolerable.

SIDE EFFECT 29. What are some possible side effects of bortezomib?

It is important to remember that everyone's reaction to treatment will be different. The frequency and severity of side effects increase with higher dosage. Side effects are usually temporary and should subside when treatment stops. The most common side effects of bortezomib include:

- Nausea, vomiting, constipation, or diarrhoea
- Low red blood cell count (anaemia), which can cause lethargy and shortness of breath
- Low white blood cell count (neutropenia), which increases the risk of infection and can be life threatening
- Low platelet count (thrombocytopenia), which can lead to bruising, bleeding, and slower healing of cuts
- Fatigue or muscle weakness
- Low blood pressure
- Peripheral neuropathy (pain, numbness, or tingling in the hands and feet)
    - Some patients may also have pre-existing peripheral neuropathy from previous treatment. Measures can be taken to lessen the risk of this side effect (eg, SC bortezomib is less likely to cause this symptom)

Most symptoms are manageable with early detection and intervention, so you must report the symptoms to your doctor when you first notice them.

HEALTH 30. What is thalidomide?

Thalidomide (Thalomid) is an immunomodulatory drug that supports the body's immune system by inducing immune responses, enhancing the ability of immune cells (e.g. T cells) to kill myeloma cells, and inhibiting inflammation. It also inhibits the growth of blood vessels on which cancer cells depend for sustenance and growth.

Oral thalidomide is indicated for use at various points over the course of the disease. The agent can be used as initial therapy in patients alone or in combination with other anti-myeloma drugs as part of a more complex multidrug regimen. Additionally, it can be used as maintenance and in cases of relapsed or refractory multiple myeloma.

The length of treatment with thalidomide varies from patient to patient. Increasing the dose slowly and managing side effects may help individuals cope with treatment. Once response has been achieved, the dose is usually reduced for maintenance therapy. If no response is achieved, combinations of other drug treatments may be added.

SIDE EFFECT 31. What are the possible side effects of thalidomide?

It is important to remember that everyone's reaction to treatment will be different. The most common side effects of thalidomide include:

- Nausea, vomiting, constipation or diarrhoea
- Fatigue or muscle weakness
- Peripheral neuropathy (pain, numbness or tingling in the hands and feet)
- Blood clots (patients may be required to take a blood-thinning agent)
- Swelling

Most symptoms are manageable with early detection and intervention, so you must report the symptoms to your doctor when you first notice them.

Thalidomide can have adverse effects on a developing foetus, so it is not recommended to be taken immediately before conception or during pregnancy.

HEALTH 32. What is lenalidomide?

Lenalidomide (Revlimid/Lenli) is another oral immunomodulatory drug that supports the function of the immune system in destroying cancer cells, similarly to thalidomide. Lenalidomide is used to treat all stages of multiple myeloma, including induction, maintenance and relapsed/refractory disease, alone or in combination with other drugs.

Lenalidomide is a popular choice for multiple myeloma treatment as it is effective in a wide range of patients. Moreover, many treatment combinations that include lenalidomide also serve as a backbone for adding further agents to bolster treatment. It is also indicated for use as maintenance therapy following high-dose chemotherapy and stem cell transplantation.

Dosing varies depending on whether lenalidomide is given in combination with other agents or as maintenance therapy following stem cell transplant. While it is chemically similar to thalidomide, it has been shown to be more potent, with fewer side effects.

SIDE EFFECT 33. What are the possible side effects of lenalidomide?

Lenalidomide is generally well tolerated by patients and has fewer side effects than thalidomide. The most common side effects of lenalidomide include:

- Diarrhoea or abdominal pain
- Low red blood cell count (anaemia), which can cause lethargy and shortness of breath
- Low white blood cell count (neutropenia), which increases the risk of infection and can be life threatening
- Blood clots (patients may be required to take a blood-thinning agent)
- Fatigue or muscle weakness
- Rash
- Shortness of breath

Most symptoms are manageable with early detection and intervention, so you must report the symptoms to your doctor when you first notice them.

Lenalidomide can have adverse effects on a developing foetus, so it is not recommended to be taken immediately before conception or during pregnancy.

HEALTH 34. What is pomalidomide?

Pomalidomide (Pomalyst) is a potent oral immunomodulatory drug usually used in patients with multiple myeloma who have received at least two prior therapies and yet demonstrate disease progression. It has been shown to be effective in patients with relapsed or refractory disease and in those with high-risk multiple myeloma.

This drug binds to a protein in multiple myeloma cells that then triggers cell death. It can also stimulate the patient's immune system and affect the blood vessels feeding the cancerous cells.

SIDE EFFECT 35. What are the possible side effects of pomalidomide?

Common side effects of pomalidomide include:

- Fatigue or muscle weakness
- Low red blood cell count (anaemia), which can cause lethargy and shortness of breath
- Low white blood cell count (neutropenia), which increases the risk of infection and can be life threatening
- Low platelet count (thrombocytopenia), which can lead to bruising, bleeding and slower healing of cuts
- Swelling of the hands or feet
- Peripheral neuropathy (pain, numbness, or tingling in the hands and feet)
- Nausea, vomiting, constipation or diarrhoea
- Shortness of breath
- Fever or headache

Most symptoms are manageable with early detection and intervention, so you must report the symptoms to your doctor when you first notice them.

Pomalidomide may cause harm to a developing foetus, so it is not recommended to be taken immediately before conception or during pregnancy.

36. What is carfilzomib?

Carfilzomib (Kyprolis) is a next-generation proteasome inhibitor. Proteasomes in cancerous cells play an important role in regulating cell growth and function by controlling protein breakdown. By blocking the activity of proteasomes, carfilzomib disrupts processes related to the growth and survival of cancer cells; they also stop producing chemicals that stimulate other cancer cells. Cancer cells are more sensitive to these effects than normal cells, so the cancer cells die while normal cells are able to recover.

Carfilzomib can be used as a single agent or in combination with treatments such as daratumumab, lenalidomide, and low-dose dexamethasone to treat patients with relapsed or refractory myeloma who have previously received one or more lines of therapy (e.g. bortezomib or lenalidomide). Carfilzomib is administered by IV infusion, sometimes in conjunction with other IV fluids to reduce side effects. It has been shown to be effective in patients with high-risk multiple myeloma and can be given to those with reduced kidney function.

37. What are the possible side effects of carfilzomib?

Possible side effects depend on patient history, stage of cancer and treatment combinations. Common side effects of carfilzomib include:

- Fatigue or muscle weakness
- Low red blood cell count (anaemia), which can cause lethargy and shortness of breath
- Low white blood cell count (neutropenia), which increases the risk of infection and can be life threatening
- Low platelet count (thrombocytopenia), which can lead to bruising, bleeding and slower healing of cuts
- Swelling of the hands or feet
- Nausea, vomiting, constipation or diarrhoea
- Shortness of breath
- Fever or headache

Most symptoms are manageable with early detection and intervention, so you must report the symptoms to your doctor when you first notice them.

Carfilzomib may cause harm to a developing foetus, so it is not recommended to be taken immediately before conception or during pregnancy.

HEALTH 38. What is ixazomib?

Ixazomib (Ninlaro) is a second-generation oral proteasome inhibitor. It is approved for use combined with lenalidomide and low-dose dexamethasone in patients with multiple myeloma who have received at least one prior therapy.

Proteasomes play an important role in regulating cell growth and function by controlling protein breakdown. By blocking the activity of proteasomes, ixazomib disrupts processes related to the growth and survival of cancer cells; they also stop producing chemicals that stimulate other cancer cells. Cancer cells are more sensitive to these effects than normal cells, so the cancer cells die while normal cells are able to recover.

SIDE EFFECT 39. What are the possible side effects of ixazomib?

Possible side effects heavily depend on the drug combination with which ixazomib is administered. Common side effects of ixazomib include:

- Low red blood cell count (anaemia), which can cause lethargy and shortness of breath
- Low white blood cell count (neutropenia), which increases the risk of infection and can be life threatening
- Low platelet count (thrombocytopenia), which can lead to bruising, bleeding and slower healing of cuts
- Swelling of the hands or feet
- Peripheral neuropathy (pain, numbness, or tingling in the hands and feet)
- Nausea, vomiting, constipation or diarrhoea
- Back pain

Most symptoms are manageable with early detection and intervention, so you must report the symptoms to your doctor when you first notice them.

Ixazomib may cause harm to a developing foetus, so it is not recommended to be taken immediately before conception or during pregnancy.

40. What is daratumumab?

Daratumumab (Darzalex) was the first monoclonal antibody approved for use in multiple myeloma. This antibody works by binding to a protein found on multiple myeloma cells, which then slows cell growth and aids the immune system in seeking and destroying these cells. It can be administered by IV infusion or SC injection for newly diagnosed (for both transplant eligible and ineligible), relapsed or refractory patients.

41. What are the possible side effects of daratumumab?

Common side effects of daratumumab include:

- Infusion reactions
- Low red blood cell count (anaemia), which can cause lethargy and shortness of breath
- Low white blood cell count (neutropenia), which increases the risk of infection and can be life threatening
- Low platelet count (thrombocytopenia), which can lead to bruising, bleeding and slower healing of cuts
- Fatigue or muscle weakness
- Back pain or joint pain
- Fever, chills, dizziness, or insomnia
- Swelling of the hands or feet
- Peripheral neuropathy (pain, numbness, or tingling in the hands and feet)
- Nausea, vomiting, constipation or diarrhoea
- Shortness of breath

Most symptoms are manageable with early detection and intervention, so you must report the symptoms to your doctor when you first notice them.

Daratumumab may cause harm to a developing foetus, so it is not recommended to be taken immediately before conception or during pregnancy.

HEALTH 42. What are steroids?

Dexamethasone and prednisolone are steroids commonly used in the treatment of all stages of multiple myeloma. Oral steroids are usually used as part of a combination treatment with other novel agents such as a proteasome inhibitor (bortezomib) or an immunomodulatory drug (thalidomide or lenalidomide).

In high doses, steroids can kill multiple myeloma cells themselves. They decrease inflammation and stop white blood cells from flowing to the disease-affected areas, which also helps relieve pain and pressure. Additionally, steroids may be used to reduce nausea and vomiting caused by chemotherapy and other forms of treatment.

Steroid treatment can result in short and long term side effects. Side effects include high blood glucose, weight gain, sleeping problems and mood changes. Over time, steroid treatment may suppress the immune system and weaken bones. However, these side effects usually disappear after treatment.

HEALTH 43. What are bone-modifying agents?

A common complaint of multiple myeloma patients is bone pain and fractures caused by the destruction of bone material. Preventing skeletal-related events by using bone-modifying agents reduces fracture risk and the need for surgery or radiation therapy.

Bisphosphonates are used to treat bone resorption. They work by slowing the bone destruction process and help strengthen the bones. Bisphosphonates commonly used in cases of multiple myeloma include zoledronic acid (Zometa) and pamidronate (Aredia). These are usually administered by IV infusion every month. Pamidronate is given over a span of 2–4 hours, while zoledronic acid is given over the course of 15 minutes. Side effects in a minority of people include flu-like symptoms, fever, headache and pain in muscles or joints.

Denosumab (Xgeva) is also used for multiple myeloma and is administered by SC injection. Denosumab works to prevent bone resorption by blocking a specific receptor in the body. This in turn, decreases bone breakdown and hypercalcaemia. This can also increase bone mass and strength. Common side effects include fatigue, muscle weakness, nausea and reduced phosphorus levels in the blood.

HEALTH 44. What is radiation therapy?

Radiation therapy, or radiotherapy, uses high-energy radiation to shrink tumours and kill cancer cells in multiple myeloma. X-rays, gamma rays, and charged particles are types of radiation used for cancer treatments.

A machine is used to deliver radiation therapy for multiple myeloma from outside the body (external-beam radiation therapy). Rays may be directed at a particular area of the bone (local radiation), a larger part of the body, or the entire body. Radiation may also be used to treat areas of bone damaged by cancer that have not been responding to chemotherapy and are causing pain.

In high doses, local radiation therapy is the most common treatment for solitary plasmacytomas in bone or soft tissue. In low doses, local radiation therapy can be used to relieve pain or treat bone fractures and spinal cord compression.

SIDE EFFECT 45. What are some possible side effects of radiation therapy?

Radiation therapy can cause both early (acute) and late (chronic) side effects. Acute side effects occur during treatment, while chronic side effects occur months or even years after the treatment ends. The side effects that develop depend on the area of the body that underwent radiation therapy, the dosage given per day, the total dosage given, the patient's general medical condition, and other treatments administered at the same time.

The acute side effects of radiation therapy are caused by damage to rapidly dividing normal cells in the area around the treatment site. Examples include:

- Damage to salivary glands
- Hair loss (when the head or neck is being treated)
- Urinary problems (when the lower abdomen is being treated)
- Fatigue, loss of appetite and nausea
- Skin irritation and blistering

Most acute side effects disappear after treatment ends, although some (e.g. damage to the salivary glands) can become permanent.

Chronic side effects of radiation therapy may occur, depending on the area of the body being treated, such as:

- Fibrosis (the replacement of normal tissue with scar tissue, leading to restricted movement of the affected area)

- Damage to the bowels, causing diarrhoea and bleeding
- Memory loss
- Infertility
- Another cancer caused by radiation exposure (in very rare cases)

46. Are there any traditional Chinese medicines/acupuncture techniques that can help improve my condition?

Doctors do NOT recommend taking any traditional Chinese medicine or receiving acupuncture during multiple myeloma treatment, as it is unclear whether these will interfere with chemotherapy. Alternative therapies may be particularly unsafe in certain patients (e.g. those with low platelet counts), so you should always consult your doctor when considering a new therapy. Instead, you may be referred to a physiotherapist or occupational therapist to learn about ways to better deal with your condition.

47. What is a clinical trial?

Clinical trials are research studies of new methods in the prevention, screening, or treatment of people with serious diseases such as cancer. Clinical trials are designed to assess:

- If a new medication is safe and effective for a specific disease
- If a current medication is safe and effective for a new indication/disease
- If new treatments are better than available standard treatments

Importantly, clinical trials can occur only after satisfactory information has been gathered from nonclinical research conducted in a laboratory. In Singapore, clinical trials involving patients are approved by the institutional ethics review board for the trial and the Health Sciences Authority of Singapore (HSA). This is done to ensure protection of your health and safety.

48. What are the current clinical trials available?

At any given time, there are multiple clinical trials studying new drugs and regimens for the treatment of multiple myeloma at this centre. You may find more information about the latest trials on the NCIS website (https://www.ncis.com.sg/Research-and-Education/Clinical-Trials/Pages/default.aspx), or ask your doctor which you are eligible for.

49. Why should I consider joining a clinical trial?

Your doctor may ask if you would like to participate in a multiple myeloma clinical trial should there be any that are suitable for your condition. Each trial has its own set of criteria to determine a participant's suitability. The most common criteria used to determine suitability for participation are age, gender, type and stage of disease, treatment history, other medical conditions and current medications.

If you choose to participate in a clinical trial, you may be one of the first few patients to benefit from a new treatment method. You have the opportunity to contribute to the future of science and treatment for multiple myeloma. Should you be offered the opportunity to partake, a doctor and a clinical research coordinator will explain the risks, benefits and process of the trial to you in greater detail.

50. How is treatment response assessed?

The International Myeloma Working Group (IMWG) has developed a set of response criteria to assess treatment effectiveness or determine whether the patient is having relapsing or progressive disease. You can refer to the table below for reference:

Response	IMWG criteria
Stringent complete response (SCR)	◆ CR as defined below plus normal free light chain (FLC) ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
Complete response (CR)	◆ Negative immunofixation on the serum and urine, disappearance of any soft tissue plasmacytomas, and < 5% plasma cells in bone marrow
Very good partial response (VGPR)	◆ Serum and urine M-protein detectable by immunofixation but not on electrophoresis, or > 90% reduction in serum M-protein plus urine Mprotein < 100 mg/24 h
Partial response (PR)	◆ > 50% reduction in serum M-protein and reduction in 24-hour urinary Mprotein by > 90% or to < 200 mg/24 h ◆ If serum and urine M-protein are unmeasurable, a > 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria ◆ If serum and urine M-protein are not measurable and serum FLC assay is also not measurable, > 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was > 30% ◆ In addition to the above criteria, if present at baseline, a > 50% reduction in the size of soft tissue plasmacytomas is also required
No change or stable disease	◆ Not meeting criteria for CR, VGPR, PR or progressive disease

Progressive disease	Increase of > 25% from lowest response value in any one or more of the following: ◆ Serum M-component (absolute increase > 0.5 g/dL) ◆ Urine M-component (absolute increase > 200 mg/24 h) ◆ Absolute increase in difference between involved and uninvolved FLC levels > 10 mg/dL (only in patients without measurable serum and urine M-protein levels) ◆ Absolute bone marrow plasma cell percentage > 10% ◆ Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas ◆ Development of hypercalcaemia (corrected serum calcium > 11.5 mg/dL [> 2.65 mmol/L]) that can be attributed solely to the plasma cell proliferative disorder
Relapse	Clinical relapse requires one or more direct indicators of increasing disease and/or end-organ dysfunction (CRAB features). Not used in calculation of time to progression or progression-free survival but listed here as something that can be reported optionally or for use in clinical practice ◆ Development of new soft tissue plasmacytomas or bone lesions ◆ Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion ◆ Hypercalcaemia (> 11.5 mg/dL [> 2.65 mmol/L]) ◆ Decrease in haemoglobin of > 2 g/dL (> 1.25 mmol/L) ◆ Rise in serum creatinine by 2 mg/dL or more (177 mmol/L or more)
Relapse from CR (to be used only if the endpoint studied is disease-free survival)	Any one or more of the following: ◆ Reappearance of serum or urine M-protein by immunofixation or electrophoresis ◆ Development of > 5% plasma cells in the bone marrow ◆ Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion or hypercalcaemia)

51. What is a stem cell transplant?

A stem cell transplant is sometimes offered to multiple myeloma patients to provide new, healthy cells from a donor (allogeneic) or from their own blood (autologous).

Autologous Versus Allogeneic Transplants

Autologous transplants (see Figure 5) refer to stem cells being collected from the patient's own bone marrow or peripheral blood before high-dose chemotherapy or radiation therapy which is used to kill the cancer cells. When complete, the stem cells are inserted back into the patient's bloodstream through a vein.

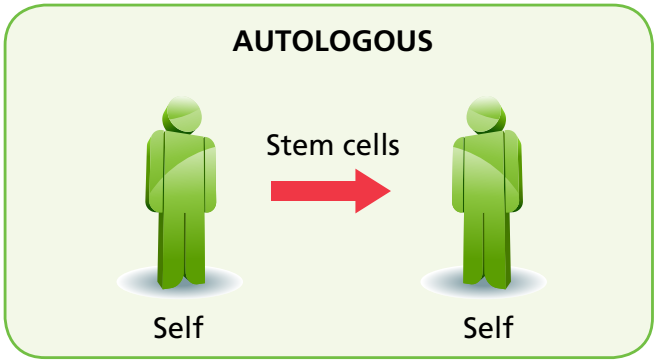


Figure 5

In allogeneic transplants (see Figure 6), the patient receives stem cells from another person whose cells are closely matched to the patient's cell type (e.g. from a relative). Allogeneic transplants are no longer routinely carried out.

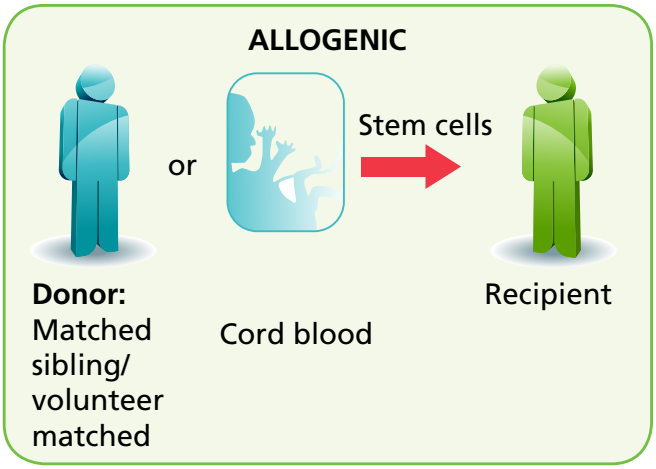
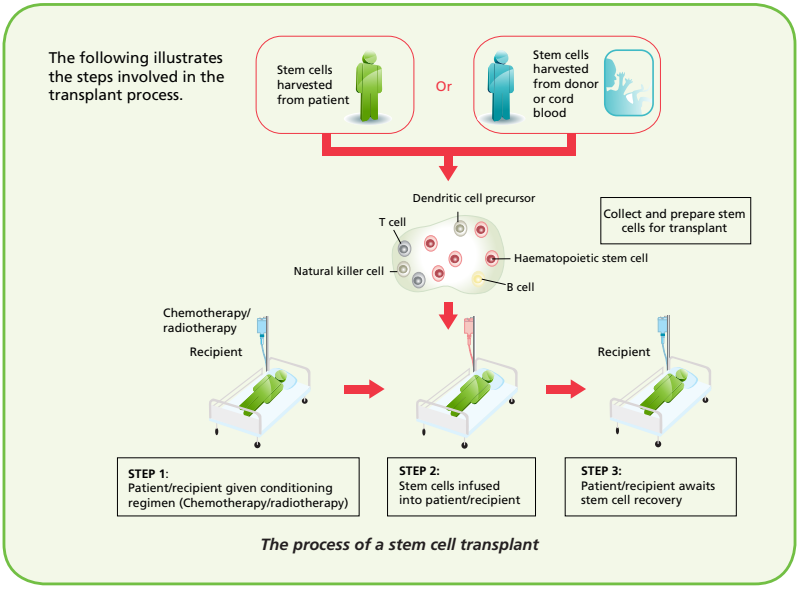


Figure 6

The Process

The following diagram illustrates the process of stem cell transplantation briefly.



The process of a stem cell transplant

Step 1: Stem Cell Mobilisation

The first step involves the collection of stem cells. In stem cell mobilisation, stem cells are transported from the bone marrow into the bloodstream, where they can be easily collected. The two techniques used for mobilisation are:

1) Growth factor injection: Granulocyte colony-stimulating factor (GCSF) stimulates the bone marrow to increase the production of white blood cells

2) GCSF plus chemotherapy: Certain types of chemotherapy can cause stem cells to move out of the bone marrow and into the bloodstream for easy collection; they may also help in the removal of some cancer cells

Step 2: Stem Cell Collection (Apheresis)

This process is carried out via a central venous catheter, which is inserted through the skin into a large vein near the groin or forearms. The patient's blood is then passed through an apheresis machine, which removes the stem cells before returning the blood to the patient's body. This process takes 4–6 hours per session, and patients may require several sessions to collect adequate numbers of stem cells.

Step 3: Conditioning

High-dose chemotherapy is administered to the patient to destroy as many cancer cells found in the body as possible.

Step 4: Stem Cell Infusion

The stem cell infusion process is similar to that of a blood transfusion. Bags of stem cells are infused into the patient through a vein over the span of 1–2 hours.

Side Effects

The side effects of transplants are similar to those of chemotherapy and radiation therapy, only more severe. Low blood counts after transplant mean that the immune system is weakened, so the patient is at serious risk of infections and bleeding. Hence, it is necessary to practise good hygiene and minimise exposure to bacteria or viruses post-transplant.

Graft-versus-host disease (GvHD) is also a serious complication whereby new immune cells from a donor attack the patient's cells. You will be monitored closely by your doctor post-transplant to keep a close eye on your progress and treat any complications early.

52. Why do I need to go through stem cell transplantation?

High-dose chemotherapy combined with autologous stem cell transplantation is now a standard therapy for patients with multiple myeloma after induction therapy. The activity of multiple myeloma cells and the action of treatments can decrease the function of the bone marrow, where white blood cells are made. A stem cell transplant can reinforce the bone marrow to make healthy cells again.

Compared with chemotherapy alone, a stem cell transplant can provide significant remission; overall survival and progression-free survival of patients are prolonged by several years. However, it does not cure the cancer, which can sometimes return.

Eligibility for stem cell transplantation is based on the patient's stage of disease, how fast it is growing, previous treatments, age and general health status.

53. What is CAR-T therapy?

Chimeric antigen receptor T-cell (CAR-T) therapy is a type of immunotherapy that helps the patient's own immune system target and kill cancer cells. CAR-T therapy is also a type of cell-based gene therapy because it involves altering the genes inside specific immune cells to help them attack the cancer.

When a patient is undergoing CAR-T therapy, immune T cells are removed from the blood and genetically altered in a laboratory so that they have specific receptors on their surface that attach to cancer cells. The T cells are multiplied and inserted back into the patient's blood to seek out the cancer cells and help the immune system attack them. This treatment can have serious side effects, so your healthcare team will watch you closely for several weeks after therapy.

54. What is BiTE therapy?

Bispecific T-cell engager (BiTE) is a new immunotherapy approach that helps the patient's own immune system target and kill cancerous multiple myeloma cells. BiTEs are a type of modified antibody with two arms: one arm of the antibody attaches to a specific protein on the cancer cell, while the other arm attaches to T cells and activates the patient's immune cells to kill the cancer cell.

BiTE therapy is different from CAR-T therapy as the product is directly administered to the patient. It does not require T cells to be extracted from the patient for genetic alteration, as with CAR-T therapy. There are several BiTE antibody products (some still in trial phases), and your doctor will explain which is suitable for you.

Survivorship and Maintenance Therapy

55. What are consolidation and maintenance therapy?

After stem cell transplant, some patients may be given additional cycles of chemotherapy. This is known as consolidation therapy, which aims to further reduce the disease and help achieve a complete treatment response.

All patients (with or without a stem cell transplant) will be given long periods of low-dose treatment (sometimes for years) usually involving lenalidomide, bortezomib, or thalidomide. This is called maintenance therapy, and the aim of it is to delay potential disease relapse.

Clinical trials have shown the benefits of both consolidation and maintenance therapies. However, as with all treatments, there are side effects. Some of these therapies are also costly. It is important to consider all these factors and ask your doctor for advice when deciding on treatment.

56. What vaccinations are recommended after completing active treatment?

Vaccinations are essential as patients with multiple myeloma have an increased risk of infections. Patients usually have weakened immune systems from the growth of cancer cells in the bone marrow, compounded by the immunosuppressive effects of active chemotherapy and radiation therapy. It is therefore considered particularly important to vaccinate multiple myeloma patients against frequently encountered pathogens after treatment.

However, you should not have immunisations with live vaccines while having cancer treatment and for a certain time after. Different recommendations also apply to patients undergoing stem cell transplants. Talk to your doctor to learn more about which vaccinations you will need and when they should be administered.

57. How do I move on to life after cancer?

Patients who have completed cancer treatment face a new chapter in their journey with multiple myeloma. Your healthcare team will be at hand to help you at every step of the way. There are many dedicated programmes available for patients at various stages:

- Patient-led multiple myeloma support groups can help people going through similar experiences by sharing experiences and information

- During maintenance treatment or after stem cell transplant, you may be referred to a survivorship service, where an advanced practice nurse can help you on your journey to recovery

- For patients in remission, a dedicated nurse navigator can help you with your treatment journey

There are several vital topics on which your survivorship nurse will support and educate you after multiple myeloma treatment, including:

- Bone health: Your nurse will regularly monitor your bone health and may recommend dietary changes, supplements, medications and exercises to minimise the risk of skeletal-related events

- Health maintenance: Routine screening and management of other conditions can help maintain optimal health. Your nurse will educate you on risk factors and management options for common diseases after multiple myeloma

- Renal health: Kidney dysfunction is a common feature of multiple myeloma and is often worsened by treatment. It can increase the risk of other complications, so your nurse will identify kidney damage and recommend appropriate interventions

- Mobility and safety: Common consequences of therapy include fatigue, weakness, bone loss, bone pain and decreased mobility. Some elderly patients are prone to falling, which may cause fractures. Your nurse can assess risk and recommend appropriate interventions to restore safe mobility

- Sexual health: Sexual dysfunction can often occur as a side effect of treatment or a result of other diseases. Psychological issues and physical changes can also contribute. The nurse can provide a risk assessment and education for patients and their partners

58. How do I support my psychological health after cancer?

Individuals cope differently after multiple myeloma. Patients sometimes live with the fear of cancer coming back, while others report feelings of anger, anxiety or depression. These are common and are all part of the process of adjusting to life after cancer.

Here are some tips that have helped patients deal with life after cancer:

- Learn about the services available to you and the steps you can take to give yourself a greater sense of control

- Patients often feel a sense of isolation. Express your feelings to trusted friends, family or counsellors. Being open and dealing with emotions helps many people feel less worried

- Patient support groups provide an informal and comfortable atmosphere to share experiences and information, as members will often be facing the same issues

- Try and live in the present moment instead of thinking about the possibility of the cancer returning in the future. Be aware that you don't have control over cancer recurrence
- Knowledge of lingering treatment effects or the possibility of cancer returning can often help patients deal with feelings of fear or anxiety, so ask your doctor any questions you may have
- Try and stay as healthy as possible to give your body the best chance of recovery. Make healthy changes to your diet, stop smoking or try exercising
- Take time for yourself and find ways to help yourself relax
- It is sometimes helpful to set yourself a target in life. Working towards the target can serve as a good source of motivation and enable a positive frame of mind

59. How does cancer affect sexual health?

Many patients experience changes in sexual health during and after cancer treatment. Sexual problems can be caused by common cancer treatment side effects such as fatigue, nausea, pain and hormone changes. An altered self-image of the body and emotional distress, including depression and anxiety, can also contribute. Sexual dysfunction is very common among cancer patients, and problems can persist for years after treatment ends. These changes in sexual health can negatively affect your quality of life and wellbeing.

It is very important to discuss with your healthcare team about what to expect and to continue talking about what's changing or has changed in your sexual health as you go through the procedures, treatments and follow-up care to give yourself the best possible quality of life.

At Relapse

60. What options do I have for relapsed or refractory multiple myeloma?

Many multiple myeloma patients who have completed initial treatment will experience relapse after a period of time, requiring further treatment. On the other hand, refractory multiple myeloma refers to the condition whereby the patient does not respond to the given treatment, or their condition progresses within 60 days of the last treatment.

Treatment options for patients with relapsed or refractory multiple myeloma may include stem cell therapy, the previous chemotherapy regimen, or a trial of a new regimen. Your doctor will decide the best choice of therapy for you by considering the severity of your disease, the prior treatments used and the duration of positive response to these treatments.

Please refer to question 26 to learn more about possible treatment options.

Diet/Nutrition

61. Do I need to take calcium supplements?

The accumulation of multiple myeloma cells in the bone marrow and side effects associated with treatment can lead to changes in levels of vitamins and minerals in your body. A primary symptom of multiple myeloma is the breakdown of bone, leading to high calcium levels (hypercalcaemia) in the bloodstream.

Conversely, calcium levels can be low in the remission stages of multiple myeloma, especially after chemotherapy and other treatments. Patients in remission may be directed by their doctor to take daily calcium supplements or eat calcium-rich foods to reinforce bone health.

However, do not begin taking supplements without first consulting your doctor as too much calcium in the bloodstream can be dangerous.

62. What precautions in diet and exercise should I take while on treatment?

Eating a healthy diet, maintaining regular exercise and making healthy lifestyle choices can help patients with multiple myeloma, both mentally and physically.

A healthy diet can help you maintain your energy and strength during treatment and aid recovery after cancer. Some treatments can affect how much and what you want to eat. In these cases, it is important to eat what you can, and when you can to help keep your energy levels up.

Depending on the symptoms and side effects, you may need to alter your intake of specific vitamins and minerals (e.g. for anaemia or to support your kidneys and immune system). In these cases, your doctor will advise you on what foods to eat and how to supplement your diet.

Using healthy eating strategies throughout treatment can help you keep your nutrition on track:

- Eat small, frequent meals throughout the day: This will ensure enough energy to fuel your body throughout the day. Try eating 5–6 small meals, or once every 3 hours
- Choose foods that are easy on your stomach: Bland foods will help avoid nausea caused by treatment. Avoid food that is fried, spicy or that has strong odours
- Include protein-rich foods: Protein is essential for the recovery and maintenance of the body. Good sources of protein include:
  - Lean meats such as chicken, fish and turkey
  - Eggs
  - Low-fat dairy products such as milk, yoghurt and cheese
  - Nuts and nut butter
  - Beans
  - Soy foods
- Choose whole grains: These are a good source of carbohydrates and fibre for energy. Good sources of whole grains include:
  - Oatmeal
  - Whole-wheat bread
  - Brown rice
  - Wholegrain pasta
- Eat a variety of fruits and vegetables: These offer antioxidants and vitamins to help support the body. Try eating a minimum of five fruits and vegetables a day
- Choose healthy fats: Healthy fats include olive oil, avocados, nuts and seeds. Avoid fried, greasy and fatty foods

- Limit added sugars: Foods high in added sugars provide little nutritional benefit
- Stay hydrated: Drinking adequate amounts of water is essential for renal function
- Wash and prepare food safely: This can help reduce the risk of infection. Wash your hands when cooking, use separate cutting boards and knives for raw meat, and cook food thoroughly

As your immune system may be weakened by treatment, you must stay away from foods that could make you sick, such as:

- Raw meat or fish (e.g. sushi)
- Runny eggs
- Unpasteurised milk or drinks
- Unwashed fruits and vegetables

Patients are also recommended to engage in gentle exercises such as walking or cycling during and after treatment to help combat fatigue. If you are suffering from severe pain, you should consult your doctor on suitable exercises for your condition. The weakened immune system during treatment and post-transplant means that swimming is not recommended as you may develop infections. You should also avoid strenuous exercises such as weightlifting and contact sports such as rugby.

Abbreviations

BiTE	Bispecific T-cell engager
CAR-T	Chimeric antigen receptor T-cell
CR	Complete response
CRAB	Calcium elevation, renal failure, recurrent infection, anaemia, bone pain and bleeding
DC	Dendritic cell
FLC	Free light chain
GCSF	Granulocyte colony-stimulating factor
GvHD	Graft-versus-host disease
IMWG	International Myeloma Working Group
IV	Intravenous
HSA	Health Sciences Authority of Singapore
HSC	Haematopoietic stem cell
MDE	Myeloma-defining event
NCIS	National University Cancer Institute Singapore
NK	Natural killer
PR	Partial response
SC	Subcutaneous
sCR	Stringent complete response
SMM	Smouldering multiple myeloma
VGPR	Very good partial response

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https://www.cancer.net

Supportive Care

63. Summary of patient journey

The Multiple Myeloma Patient Journey

Symptoms

Symptoms of multiple myeloma include:

- Bone damage
- Hypercalcaemia
- Kidney problems
- Anaemia
- Recurrent infections
- Increased bleeding

Testing and Diagnosis

To confirm the presence and stage of multiple myeloma, a doctor will perform certain tests such as:

- Blood and urine tests
- Imaging studies, such as X-ray, MRI, CT, or PET
- Bone marrow aspiration or biopsy

Treatment

Treatment for multiple myeloma can help to destroy cancerous cells and alleviate symptoms. Depending on the stage of disease, one or more of the following may be recommended:

- Drug therapy such as:
  - Proteasome inhibitors
  - Immunomodulatory drugs
  - Steroids
  - Histone deacetylase inhibitors
  - Monoclonal antibodies
  - Chemotherapy agents
  - Bone-modifying agents
- Radiation therapy
- Stem cell transplantation
- CAR-T therapy
- BiTE therapy
- Clinical trials

Remission (partial/ complete) and survivorship (end of treatment and start of maintenance)

Many patients who respond well to treatment, with the signs of cancer diminishing, will be offered maintenance therapy. A small group of patients may not require further treatment

Testing and Monitoring

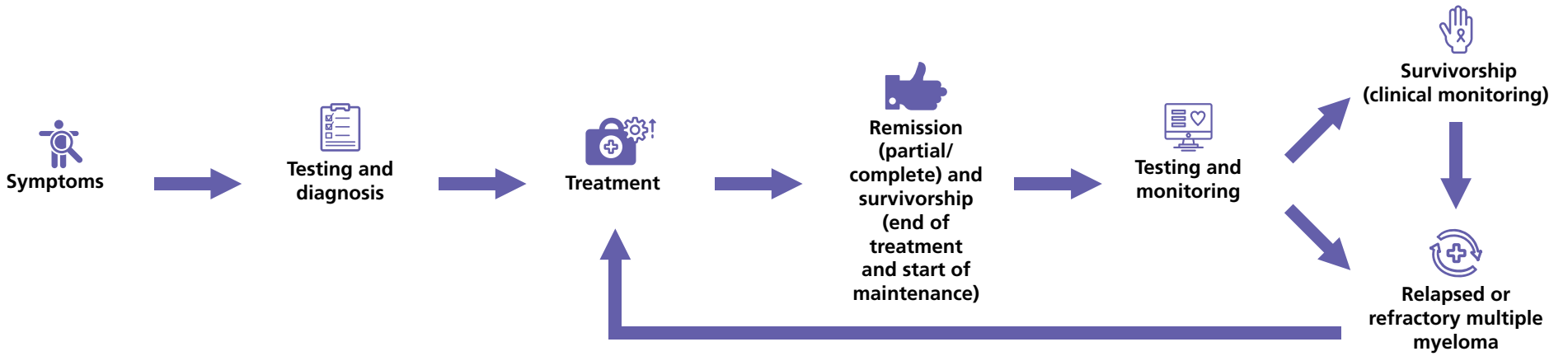
Survivorship (clinical monitoring)

Many patients remain in remission and do not require further treatment. They then progress to life after cancer

Relapsed or Refractory Multiple Myeloma

The cancer may become active or progress after a period of remission and could then require further treatment

BiTE, bispecific T-cell engager; CAR-T, chimeric antigen receptor T cell; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography



SUPPORTIVE CANCER CARE

Throughout the entire cancer journey, experienced specialists work together as a team to coordinate and support all aspects of multiple myeloma patient care. Healthcare professionals that may be involved include:

- Primary haematology doctor
- Nurse
- Research coordinator
- Nurse navigator
- Dietician
- Medical social worker
- Physiotherapist and occupational therapist

Cancer Survivorship Service
Provides holistic and personalised end-to-end support that begins at the point of diagnosis and continues through treatment, survivorship, and end-of-life care.
Tel: +65 9836 8204
Email: ncis_survivorship@nuhs.edu.sg

Patient Support Groups
Being diagnosed with cancer can be a life-changing event. Join other cancer warriors to share common concerns and emotional support.
Email: ncis_survivorship@nuhs.edu.sg

NCIS CancerLine
A free and anonymous counselling hotline managed by trained advanced practice oncology nurses.
Tel: +65 9722 0569
Operating hours: 8.30 am to 5.30 pm Mondays to Fridays
(Closed on weekends and public holidays)
Email: CancerLineNurse@nuhs.edu.sg

64. Nurse

Nurses play many crucial roles throughout the patient journey in delivering supportive care, especially in multiple myeloma. Nurses provide multiple myeloma patients and their families with information and education on their condition and treatment options so that they can make informed decisions. Nurses often carry out physical examinations to monitor disease status and administer cancer treatment prescribed by doctors, such as drug therapy. Some nurses may also be involved in research and clinical trials investigating outcomes related to multiple myeloma.

At our centre, we have specialist advanced practice nurses who work collaboratively with doctors, using their advanced knowledge and clinical skills to diagnose, anticipate and manage complex cases. Advanced practice nurses also provide social and psychological advice and support throughout the entire patient journey. These nurses have a particular focus on survivorship care after remission, focusing on the long-term side effects of treatment and the transition to life after cancer. A dedicated telehealth service supported by advanced practice nurses has been set up at NCIS for patients with multiple myeloma, meaning that nurses are always at hand for advice and support. This service is focused on transitioning and re-integrating stable patients into the community for long-term care.

65. Nurse navigator

The nurse navigator is usually the first point of contact for day-to-day patient support, to help those with multiple myeloma navigate their disease and move through the healthcare system. The nurse navigator helps patients overcome barriers and provides them with resources and education about their condition and treatments. A significant part of the nurse navigator's role is to provide emotional support and empowerment to multiple myeloma patients and their families, from diagnosis to treatment and remission to relapse. A dedicated support group has also been established at NCIS for multiple myeloma patients, moderated by the nurse navigator.

The assigned nurse navigator efficiently coordinates with other members of the multiple myeloma care team to ensure that patients receive support tailored to their individual needs. They are readily contactable via the telephone hotline and can also assist patients in scheduling tests and procedures or answering common concerns and queries. At NCIS, the nurse navigator also acts as the research coordinator, providing patients with information about current clinical trials, guiding patients through the process and coordinating the study internally.

66. Research coordinator

The research coordinator facilitates the progress of clinical research from beginning to end. They help to guide patients participating in clinical trials and longitudinal studies. They also act as an internal resource for doctors and investigators at the centre conducting clinical trials, for example, if there are any queries regarding the treatment, research protocol or patient inclusion criteria. They also often help investigators navigate the complex administrative and regulatory requirements for implementing trials at the centre and ensure adherence to best practices for patient safety and optimal outcomes.

67. Dietician

Dietary issues commonly occur as a side effect of multiple myeloma or its treatment and can persist into the recovery period. For example, many patients face problems such as steroid-induced hyperglycaemia or neutropenia during their course of treatment. Certified dieticians at NCIS collaborate closely with other members of the multiple myeloma care team to personalise the patient's recommended dietary plans based on their disease and treatment side effects.

The dietitian can educate on nutritional needs and answer questions regarding decreased appetite, weight loss/gain, dry/sore mouth, nausea and vomiting. Patients then develop a close and ongoing relationship with the dietician to ensure that healthy lifestyle changes persist throughout diagnosis and treatment to life after cancer.

68. Medical social worker

Medical social workers support patients in dealing with the social, emotional and environmental problems that may come with illness or disability related to cancer. The social worker can help patients find multiple myeloma community resources and support services to cope with different types of distress. Emotional support is provided through case management, counselling and support groups. They can also provide guidance with issues such as insurance coverage and other forms of practical or financial assistance.

69. Physiotherapist and occupational therapist

Physiotherapists examine, test, and treat physical problems related to the pathology of multiple myeloma or the side effects of treatment. Some of the challenges that multiple myeloma patients face include chronic lower-back pain and impaired gait stability. Physiotherapists use various exercises, heat, cold and other methods to restore or maintain the body's strength, mobility and function. Many patients can move around independently and safely with the correct mobility aids and strengthening exercises prescribed by physiotherapists.

Similarly, occupational therapists work with patients who have functional impairments or limitations due to multiple myeloma to help them develop, recover and improve the skills needed for daily living and working. They also work to prevent disability and maintain health through treatment and education. Peripheral neuropathy is a common treatment complication of multiple myeloma that affects patients' daily activities, such as buttoning shirts or picking up objects. Occupational therapists can assess the patient's remaining functions and implement innovative tools to combat these challenges.

References

https://www.cancer.net
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The National University Cancer Institute, Singapore (NCIS) is the only comprehensive public cancer centre in Singapore treating both paediatric and adult cancers in one facility. Located at the National University Hospital (NUH), NCIS offers a broad spectrum of cancer care with expertise in prevention, screening, diagnosis, treatment, rehabilitation and palliative care.

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