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Oncology
—
Hematology

Fast Facts for Patients

Waldenström Macroglobulinemia

Karger

HEALTHCARE

Note: Abbreviations and medical terms are explained in the Glossary on page 45.

First, the facts...

1. Waldenström macroglobulinemia (shortened to WM) is a rare blood cancer.
2. WM usually progresses slowly; some people do not show symptoms for several years after diagnosis.
3. A person who does not have symptoms usually does not need treatment, but active monitoring is essential so that treatment can be started as soon as it is needed.
4. Although there is no cure for WM, different treatment options can keep the disease under control for many years in a lot of people.
5. Eventually, the treatments tend to lose their effect.
   New therapies are being tested in clinical trials across the world, with promising results.

This book provides the information you need to have an informed discussion with your healthcare professional and to help you choose how you want to manage your condition. Spaces have been provided to help you keep notes on your symptoms and concerns and record any questions you may have.

My main concerns

Make a note of anything you want to discuss with your doctor here…

What is Waldenström macroglobulinemia?

WM is a type of non-Hodgkin lymphoma known as lymphoplasmacytic lymphoma (LPL). It is a rare blood cancer in which abnormal cells build up in the bone marrow and other places.

WM most commonly affects people over 60 and slightly more men than women.

To understand WM it helps to get to know some of the terms that your doctor may use and to learn a bit about the biology of the disease. Understanding what causes WM and how the disease develops will help you to ask the right questions and make good treatment choices.

Turn to page 39 to find out more about:

- normal blood cell production and what goes wrong in WM
- a paraprotein called IgM
- a condition called MGUS that can develop into WM
- the gene mutations that produce abnormal proteins in your body.

The abbreviations and medical terms used throughout this book are also explained in the Glossary and abbreviations on page 45.

How will WM affect me?

Symptoms vary from person to person depending on how the disease develops. Not everyone gets all of the symptoms. Even after diagnosis, you may not get any symptoms for many years.

Symptoms may develop because of:

- disrupted production of normal blood cells
- thickening of the blood because of high levels of IgM paraprotein, an abnormal immunoglobulin (antibody); see pages 40 and 42.
- IgM paraproteins mistakenly targeting tissues and organs
- the IgM becoming sticky or fragmented
- the IgM coating nerve cells and causing damage (peripheral neuropathy).

Over time, LPL cells fill up the bone marrow or collect in the lymph nodes or the spleen (and, rarely, in other places in the body).

Effects of having fewer healthy blood cells

Having fewer red blood cells leads to anemia, which can cause tiredness, weakness and breathlessness. This is linked with fatigue, an extreme form of tiredness that is the most common symptom of WM. A lack of white blood cells weakens the immune system, so you may tend to develop infections. A lack of platelets leads to a tendency to bruise or bleed easily, as platelets are important in blood clotting.

B symptoms

Fevers, night sweats and weight loss may be a feature of later-stage WM. You might hear them referred to as B symptoms. They happen when the LPL cells build up to the extent that their metabolic activity becomes physically noticeable through these symptoms. Tell your doctor if you start to notice these symptoms – for example, if you need to change nightclothes regularly or you have lost a significant amount of weight. You may need to start treatment.

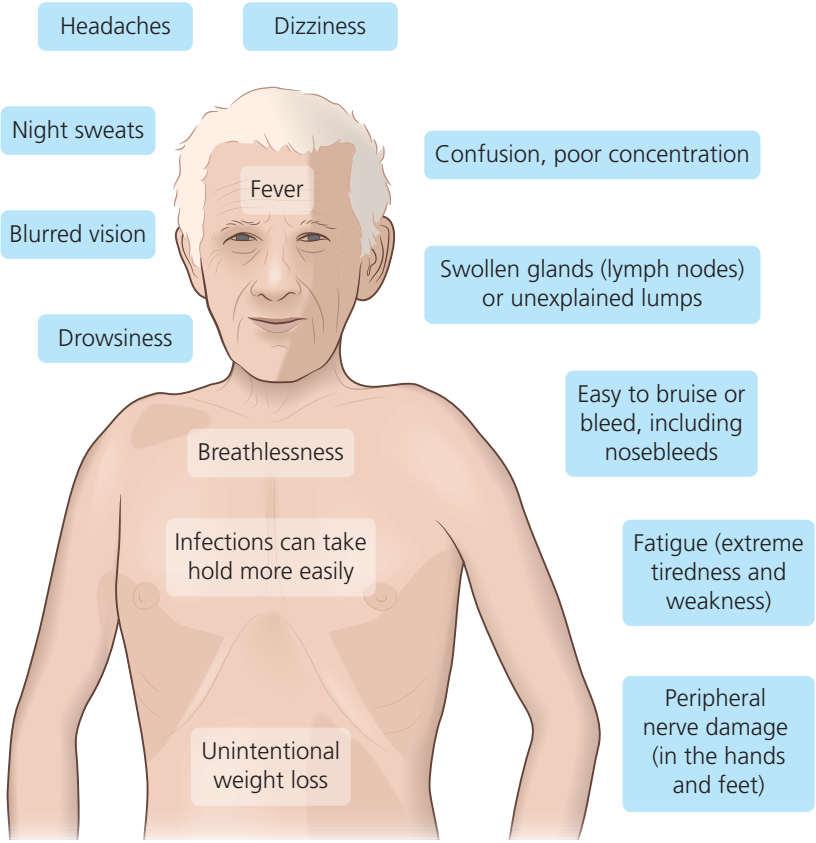
Swellings and lumps

In about a quarter of patients with WM, lymph nodes and/or the spleen may enlarge; you might notice swollen glands. Rarely, a swollen spleen can be uncomfortable or painful.

LPL cells may collect in body cavities, causing soft tissue masses (lumps) or a build up of fluid in the chest (pleural effusion). Rarely, the cells may build-up in the skeleton, causing bone pain. If these symptoms appear, the diagnosis is confirmed by taking scans and analyzing samples of tissue from a biopsy.

Some of the possible effects of WM

The effects of WM vary from person to person. You may experience some or none of these effects.

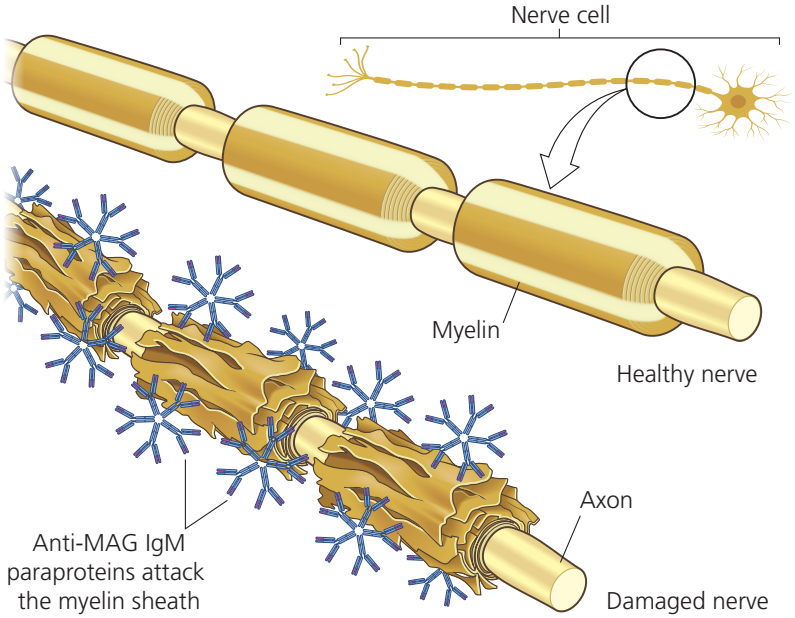


Anti-MAG neuropathy

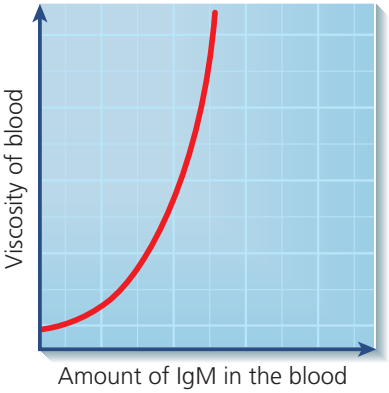
IgM paraproteins may mistakenly target tissues and organs in the body. In anti-MAG (myelin-associated glycoprotein) neuropathy, the IgM paraprotein damages the axons of nerves (neurons) or the myelin that insulates them. This can lead to numbness or tingling in the hands and feet or problems with balance if the nerve damage is in the limbs (peripheral neuropathy).

It is important to mention any of these symptoms to your doctor, especially if they are getting worse over time.

You may need tests to examine your nervous system in more detail: a scan of your brain or spinal cord, a lumbar puncture to look for signs of inflammation, nerve conduction studies to see how well your nerves are conducting electrical impulses or perhaps a nerve biopsy (under a local anesthetic).



Hyperviscosity syndrome



As the graph shows, once blood IgM paraprotein levels increase past a certain point, the blood becomes much thicker or more viscous. This is called hyperviscosity syndrome.

Symptoms include bleeding from the nose and mouth, headaches, blurred or loss of vision and dizziness. These symptoms are more likely to occur if your IgM level is over 40 g/L. Your doctor will recommend treatment if you have symptoms.

A test for blood thickness (serum or plasma viscosity) can be done in specialist laboratories.

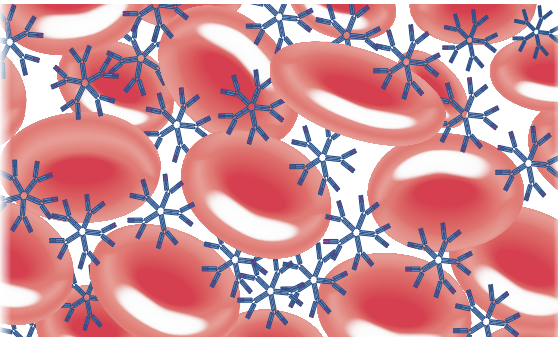
Bing–Neel syndrome

Very occasionally, LPL cells build up in the central nervous system (CNS), resulting in Bing–Neel syndrome. The symptoms are varied, but may include headaches, seizures, weakness of the facial or limb muscles, double vision, personality change and memory loss. Special tests such as brain scans and sampling of the cerebrospinal fluid by a lumbar puncture are needed to identify the cells. This rare complication can be treated if recognized promptly but requires special treatments.

Cold agglutinin disease

Cold temperatures may trigger IgM to act as a bridge between red blood cells, causing them to stick together in the cooler parts of the body, such as the hands and feet, the tip of the nose and the ear lobes. This is called agglutination and the condition is called cold agglutinin disease (CAD).

The affected areas have poor blood circulation, especially when it is cold: color changes and ulcers may develop as the skin

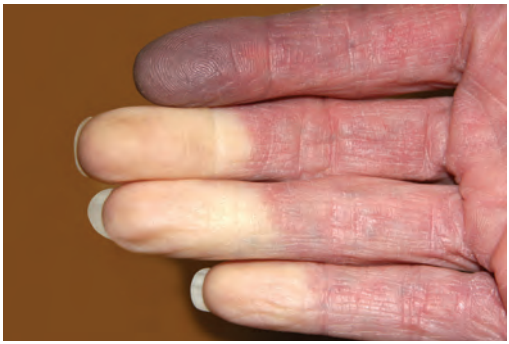


The IgM acts like a bridge between red blood cells, causing them to clump together.

breaks down. CAD also results in the breakdown of red blood cells (hemolytic anemia) due to activation of a part of the immune system called complement. This can cause bouts of fatigue and breathlessness and may cause the urine to become very dark from time to time, especially when conditions are cooler.

Cryoglobulinemia

Cryoglobulinemia is different from CAD in that IgM molecules stick to each other when circulating in cooler parts of the body, such as the hands and feet, the tip of the nose or the ear lobes. This can cause poor circulation in these areas, color changes like Raynaud's phenomenon or ulcers.

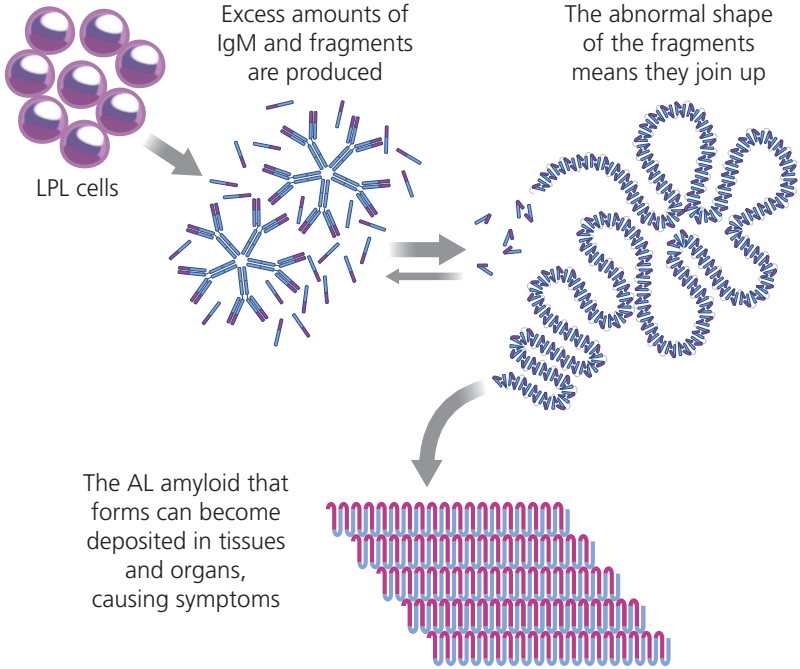


Raynaud's phenomenon can cause color changes in different parts of the body, such as the hands and feet.

A similar process can affect the joints, kidneys, skin and nerves, causing damage to these tissues. If you notice problematic cold intolerance, it is worth asking your doctor about cryoglobulinemia. Diagnosis requires a test in which the blood sample needs to be kept warm until it reaches the laboratory for analysis.

Amyloidosis

In amyloidosis, fragments of the IgM change and form an abnormal protein called AL amyloid. This can be deposited in various tissues and organs, causing them to function less well. The heart, spleen, lymph nodes, nerves, gastrointestinal tract, vocal cords and kidneys can be affected to varying degrees in different people.



Tell your doctor if you experience breathlessness, dizziness when standing up, low blood pressure, new intolerance of blood pressure medication, diarrhea, weight loss or symptoms of peripheral neuropathy (such as numbness, tingling or pain in your hands or feet).

AL amyloid usually builds up gradually, which often delays its detection. Tests may include blood tests to assess heart function (NT-proBNP test), urine tests to look for excess protein leakage (nephrotic syndrome), echocardiography (a type of ultrasound scan that looks at the heart and nearby blood vessels) and/or tissue

biopsy (the tissue is then examined using a stain called Congo Red, which shows the build-up of amyloid deposits). In the UK, a SAP scan may be performed at the National Amyloidosis Centre in London. Serum amyloid P component (SAP) is a normal protein in the blood that binds to amyloid deposits.

Your doctor must suspect amyloidosis is a possible diagnosis for these tests to be carried out, so it is important to report the symptoms mentioned above and ask about amyloidosis.

Transformation to aggressive non-Hodgkin lymphoma

In a small number of people, WM develops into an aggressive non-Hodgkin lymphoma in a process called high-grade transformation. Transformation means that LPL cells develop the biological characteristics of diffuse large B-cell lymphoma (DLBCL). This is usually accompanied by rapidly noticeable changes, such as new swellings, sweats and weight loss.

A tissue biopsy is needed to confirm transformation. Treatment requires intensive chemotherapy with or without stem cell transplantation or newer therapies.

My symptoms and complications

Make sure you discuss all your symptoms and complications with your doctor. Make a note of them here...

Who is in my care team?

Your care team will be led by a hematologist-oncologist, a doctor with expertise in diagnosing and treating diseases and cancers of the blood. Some hematologists treat many different kinds of blood diseases, while others specialize in blood and bone marrow cancers. If ever you feel unsure of what is being offered or why, think about getting a second opinion. It is important to feel comfortable with the options that have been recommended and to have a good understanding of what is going to happen.

Depending on your symptoms, you may be seen by other specialist doctors, such as an ophthalmologist (eyes), neurologist (nerves) and cardiologist (heart specialist).

The clinical team is also supported by:

- pathologists, who analyze bone marrow and other tissue biopsies to confirm the diagnosis
- radiologists, who analyze scans of your body.

You may also have specialist nurses in your clinical team (in the UK, you will be allocated a clinical nurse specialist). They provide support for your health, emotional and social needs and have experience of overseeing chemotherapy and other treatments.

Names/details of your care team

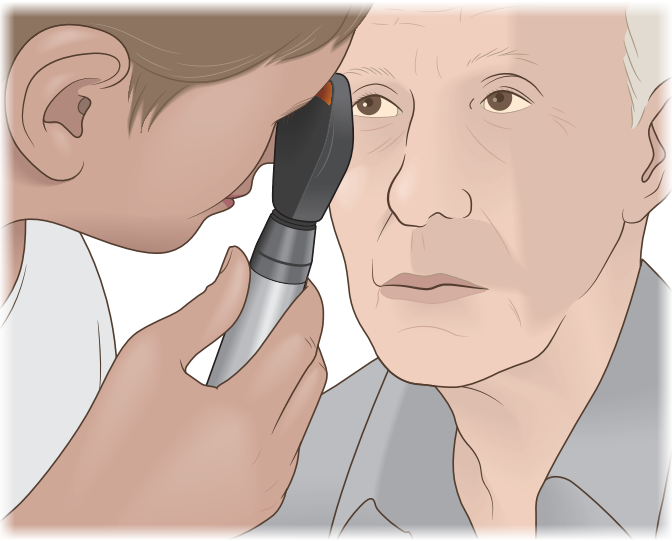
Make a note here of the names and contact details of the healthcare professionals assigned to your care...

What tests will I need to have?

Your doctor will ask about your symptoms and general health, any medication you are taking and any allergies you have.

You will be examined to assess your overall health and to look for any signs of abnormal swellings or enlarged organs.

If the doctor is concerned about high blood viscosity, they may examine the back of your eyes (retinas) with an ophthalmoscope.



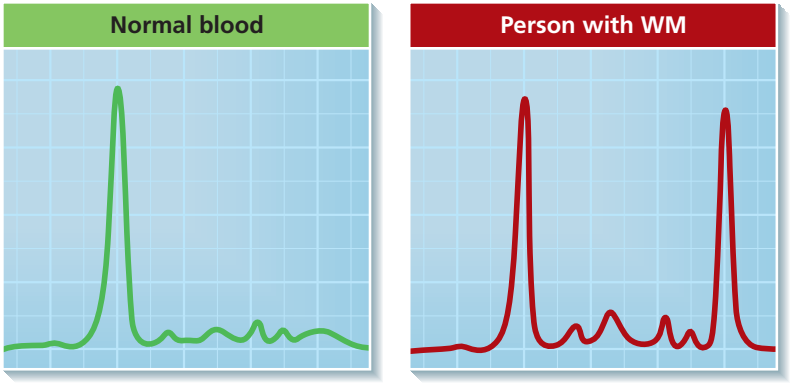
They will also examine your skin for bruising and signs of color change when cold.

If you have symptoms of a neuropathy (nerve damage), the hematologist may carry out a brief neurological examination. You may also be referred to a neurologist for specialist assessment and may have electrical studies called nerve conduction tests.

Blood tests

Blood samples will be taken for different tests.

- **Complete or full blood count:** measures different types of cells in the blood.
- **Metabolic panel:** measures different chemicals to assess the health of your kidneys, liver and bones.
- **Immunoglobulin tests:** detect excessive production of immunoglobulin (Ig) and identify IgM paraprotein. They also measure levels of IgA and IgG as these are sometimes low in WM, making sinus and bronchial infections more likely. For a better understanding of immunoglobulins, see pages 40 and 42.

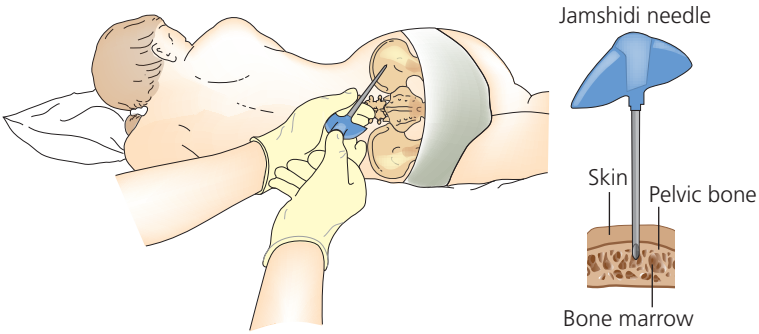


Serum protein electrophoresis shows the amount of different proteins in the blood by separating them according to their electrical charge. In WM, there is a peak that corresponds to the high amount of IgM.

- **Beta-2 microglobulin:** used in scoring systems for prognosis and may help predict how you will respond to treatment.
- **Lactate dehydrogenase:** also used in scoring systems for prognosis.
- **Serum or plasma viscosity:** used if hyperviscosity (see page 6) is suspected. The viscosity of water is 1 centipoise (cp). Normal serum viscosity is 1.4–1.8 cp. Symptoms of hyperviscosity can appear with a serum viscosity as low as 3 cp, but they usually occur when it is above 4–5 cp.

Bone marrow biopsy

As WM is a disease of the bone marrow, it is essential to take a sample of the marrow to confirm that LPL cells are present, how many there are and how much normally functioning bone marrow remains. This procedure is called a bone marrow biopsy. The samples are usually taken from the back of your hip bone (pelvis).



You will be given an injection of local anesthetic to numb the area. The doctor or nurse will then pass a needle through the skin into the bone and draw a small sample of liquid marrow into a syringe (bone marrow aspirate). After this, they will take a small core of marrow from the bone – this is called a trephine biopsy. Both samples are examined under a microscope.

The sample can be taken on the ward or in the outpatient department, and the procedure takes 15–20 minutes. You do not need to fast beforehand. It may be uncomfortable or briefly painful, but this should only last for a few seconds. You may be offered a mild sedative before the procedure or gas and air while having the procedure.

Occasionally, a shooting electrical sensation may be felt down one leg if the needle irritates a nerve but this should settle down immediately or within a few hours.

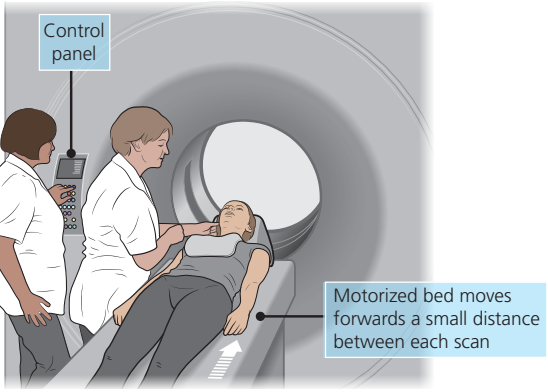
A small dressing or plaster is placed on the skin after the procedure, and you can move around straight afterward. Any tenderness usually settles in a day or two and you can take mild painkillers if you need to.

In the laboratory, a pathologist will look at the stained smear of bone marrow cells under the microscope. Liquid marrow is also extracted for flow cytometry, which sorts cell groups according to patterns of receptors on their surface.

It may take 7–10 days to get the results because of the processing involved. There may be information on genetic abnormalities, too. The presence of genetic changes (see page 44) may affect your response to treatment.

Scans

CT scan: X-ray cross-section images are taken as the body moves through the scanner. A computer combines these to produce detailed pictures. The process involves lying still for 30–45 minutes.



You may be asked to fast for 4 hours before your appointment. Before the scan, you may be given a drink or an injection into your arm. This puts a contrast medium into your body, which allows areas to be seen more clearly. You may feel a hot sensation for a few minutes afterward. If you have kidney problems, you probably will not have contrast as it can affect the kidneys.

PET-CT: glucose with a radioactive tracer is injected into a vein and a CT scan can follow the path it takes in the body. PET-CT can provide useful information if high-grade transformation is suspected. If you have diabetes, it is important that your blood sugar is well controlled at the time of the scan.

MRI: a scan that uses strong magnetic fields and radio waves to produce 3D images of your internal organs. It may be performed to investigate Bing–Neel syndrome or peripheral neuropathy. You may be moved into the scanner head first or feet first, depending on the part of your body being scanned.

TERMINOLOGY TIP

CT is computed tomography

PET-CT is positron emission tomography combined with CT scanning

MRI is magnetic resonance imaging

My questions

Make a note of any questions you have about your tests or test results...

Common feelings when diagnosed

For most people, it is a shock to be diagnosed with a very rare disease with an unpronounceable name. The prospect of having a life-limiting condition can be frightening.

Diagnosis may be a relief, though, particularly if you have had a lot of symptoms. Treatment can start to improve wellbeing.

If you do not need treatment right away, the lack of action after receiving a cancer diagnosis can be disconcerting if an active monitoring approach is recommended.

Anyone who receives a cancer diagnosis typically feels overwhelmed and powerless as they grapple with many tests and a new vocabulary surrounding the condition (see page 45). WM is a complex disease, with many strands and possible consequences.

Connecting with others

It is very helpful to find sources of reliable information and support. You can do this yourself or a family member or friend can do it. There are many sources of information available online. It is important to look at accurate and up-to-date information.

Useful resources

UK

WM UK
wmuk.org.uk

Lymphoma Action
lymphoma-action.org.uk

USA

Alliance for Cryoglobulinemia
allianceforcryo.org
allianceforcryo.org/cool-down-warm-up

Amyloidosis Foundation
amyloidosis.org

Canada

WM Foundation of Canada
wmfc.ca

International

International WM Foundation
iwmf.com

Further information about CAD:
rarediseases.org/rare-diseases/cold-agglutinin-diseasetesting.com/tests/cold-agglutinins

Helping yourself

Get a clear picture

It is recommended that you and/or a family member or friend find out what to expect after diagnosis, depending on whether you are being actively monitored, treated or monitored after receiving treatment. It is advisable to seek answers to your questions from your clinical team and keep records of your discussions, medications and treatments.

Make sure you understand why you are receiving different medications (are they part of your chemotherapy or supportive medications?). From time to time, ask your doctors to review whether you need to continue your medications, especially those that were added during your WM treatment.

Don't feel shy about asking questions to help you stay safe and well as you live with your WM. If necessary, seek a second opinion.

Minimize the risk of infections

It is important to remain vigilant about possible infections that you develop or encounter. What you do about them depends on whether you are on or off treatment, whether you have had previous treatment and, if so, how long ago. All these factors can influence the state of your immune system. This is even more crucial now in the COVID-19 era.

Accepting vaccines against viruses (flu, COVID-19) and bacteria (pneumococcus, meningococcus, *Haemophilus influenzae*) is recommended, even though it is not clear how much protection you will gain if your immune system is suppressed. It is important to AVOID ALL LIVE VACCINES, which could result in a form of the infection they are designed to prevent.

Taking sensible precautions to prevent infection, such as mask-wearing, hand-washing and avoiding crowded indoor spaces, is worthwhile.

Maintain a good all-round diet

There is no evidence that special diets are of benefit for WM. In general, a varied and wide-ranging diet is the best way to obtain the nutrients you need. At times, you may need to adapt your diet. Chemotherapy may reduce the number of white blood cells called neutrophils, so it may be helpful to stick to a 'neutropenic' diet during chemotherapy. When your blood cell counts are normal such a diet is not needed. Consult with your clinical team if you are unsure.

Certain vitamin deficiencies are common in WM, for reasons unknown. These vitamins (B12, folate, vitamin D) are easy to replace. If you are developing anemia that cannot be accounted for by a build up of LPL cells, it is worth checking your vitamin B12 and folate levels. If they are low, they can be replaced by tablets or injections. Another correctable cause of anemia in WM is iron deficiency. This can be remedied by intravenous infusions of iron.

It is also worth checking your vitamin D level yearly to ensure you have enough, as it is important in so many physiological functions, including bone health. It is one of the few vitamins worth taking regularly (unless you have a specific reason to avoid it). A reasonable dose is 1000 IU/day.

Any diet or supplement that recommends amounts that are in excess of the recommended daily allowance (RDA) should be avoided unless they are prescribed for a specific reason by a doctor. Such excesses can affect WM in ways we cannot predict, and if you are on chemotherapy they can interfere with the way the treatment works.

Keep up the exercise

Regular physical activity is beneficial for overall health. If you are living with WM, there are even more reasons to maintain your fitness to help keep your heart and lung function at good levels to tackle fatigue, stave off infections and cope better with chemotherapy treatments, if and when they are needed.

Moderate, regular exercise that is suitable for you is the best thing to aim for. This will vary from person to person. A daily walk is better than nothing at all. Apart from improving physiological fitness, it raises the spirits and, if outdoors, connects you with nature.

It is equally important not to overstretch yourself, especially during or after therapy, until you feel up to it. Having 'good' and 'bad' days is a common experience in WM and may have physical and psychological/mood origins.

If you have a medical condition, such as heart disease, high blood pressure or diabetes, it is important to seek advice from your doctor if you are unsure.

Peripheral neuropathy can impede your ability to exercise, for example if you have numbness or loss of balance or weakness in your limbs. Expert review is recommended to determine the nature and cause of the neuropathy. Appropriate treatment should be given if needed. There are many medications to help with the management of pain. Discuss your situation with your doctor, and seek out physiotherapy and occupational therapy as needed.

Rest when you need to

Fatigue is a very common symptom in WM and has many causes. Furthermore, these causes can change over time, depending on your general health, the medication you are receiving and the status of your disease. It is important to share your concerns with your clinical team so that the matter can be addressed as effectively as possible.

There are times when the best thing to do is rest. If this is the case, it is important to give yourself the time and space to do so. There is lots of information about management of fatigue. Make sure you look for guidance from reputable sources.

Active monitoring

Treatment might not be started straight away after diagnosis.

If the doctor's assessment is that treatment is not needed, you will have regular check-ups and blood tests to look for signs of progression.

If you have no symptoms, you will typically be seen in the clinic every 3–6 months for clinical review and blood tests.

Doctors use this approach because:

- there is no evidence that treating the condition before symptoms develop is advantageous
- treatments may cause side effects and suppress the immune system, so they are only recommended when benefit outweighs risk.

It can be hard to wait for symptoms to develop or for things to become worse before anything is done. It can make you feel anxious and unable to enjoy your good health while living with a cancer diagnosis. If you feel like this, it is important to talk to your clinical team and family and friends, so that you can work out a way to cope. Some of the charities listed on page 16 may offer counseling or support groups, too.

It is important to report new symptoms as they occur, even if your appointment is not due.

My concerns

If you are being actively monitored, make a note of any worries you have here and discuss them with your care team...

Starting treatment

Your doctor will consider starting treatment if:

- you start having symptoms, such as progressive fatigue, weight loss, swellings or infections
- the level of IgM in your blood is increasing rapidly or hyperviscosity develops
- your blood count changes – for example, you might develop progressively lower levels of red blood cells, white blood cells or platelets
- complications of abnormal IgM develop, such as a progressive neuropathy, cryoglobulinemia, amyloidosis or CAD.

Which treatment?

Your medical team will recommend the most suitable treatments based on:

- your test results, including which gene mutations you have
- your age and general health
- your symptoms – for example, how severe they are and whether you have neuropathy.

Treatment aims to keep you well (and improve your quality of life) with the fewest possible side effects.

Chemotherapy has been the mainstay of treatment for many years. But as a result of research and clinical trials, many new therapies are becoming available – these are called biological or targeted therapies. The best way to use novel therapies remains the focus of research (see page 38).

Blood transfusions, growth factor injections and plasma exchange may also be used to improve symptoms. These are called supportive treatments.

Types of treatment

Chemotherapy

Chemotherapy drugs destroy cancer cells, usually by stopping them from growing and dividing.

Combining different treatments can improve their effectiveness. If you are treated with just one chemotherapy drug, any side effects are likely to be mild. But you may have more side effects if you have a combination of drugs.

Most treatments for WM are given in an outpatient clinic and you would not be admitted to hospital unless complications develop. Your doctor or specialist nurse can tell you what to expect. You should always tell them if you have any side effects and talk about your concerns. Very effective medicines are available to help with side effects.

Chemotherapy-based treatment for WM is given for 4–6 months and then stops. Sometimes the condition seems slow to respond. But most people do start to improve given adequate time, and it is important to avoid switching to a new therapy too soon.

One of the most common side effects of chemotherapy is being more prone to infections. Always let your doctor or nurse know if you have any signs of an infection, such as a cough, fever, shivering or shaking, so it can be treated straight away.

The most commonly used chemotherapies for WM are listed below. They can be given as the first treatment or later for re-treatment.

Cyclophosphamide may be taken as tablets or given into a vein (intravenously). It is usually given in combination with other agents, such as dexamethasone (a steroid) and rituximab (a monoclonal antibody; see page 24) in the DRC regimen (see Combination treatment, page 24). Or it can be given as part of the CHOP regimen, which is made up of cyclophosphamide, hydroxydaunorubicin, vincristine (or oncovin) and prednisolone.

Bendamustine is given as a drip into a vein. It is usually given on days 1 and 2 of a 4-week cycle in combination with rituximab, which is given only on day 1 of the cycle. Bendamustine can be used in people who may need a stem cell transplant in the future. It is given for up to 6 cycles. Antibiotics are given with bendamustine to help avoid infections. Any blood transfusions need to be irradiated (your clinical team can explain this in more detail).

Chlorambucil is taken as a tablet and usually given for 7–10 consecutive days per month for 6–8 months. It may be given with a steroid called prednisolone and with rituximab. Chlorambucil should be avoided if a stem cell transplant is being considered as it makes it difficult to collect stem cells later. It is generally avoided in younger people.

Steroids are often used as part of the treatment as they can make chemotherapy more effective. They can be given as tablets or an injection into a vein (intravenously). Side effects include fluid retention, weight gain, restlessness, agitation and sleep disturbance, and a tendency to high blood sugar and high blood pressure. These effects are temporary and usually stop when treatment finishes.

Other noteworthy chemotherapy drugs. There are some chemotherapy drugs that are still widely used in the treatment of B-cell lymphomas, but less so in WM because of adverse effects. These include fludarabine and cladribine, which are no longer recommended because of a low risk of developing second cancers. Better alternatives to these drugs are used instead. However, these drugs may be used to treat late-stage disease that has relapsed many times to try to induce a remission when no other options are available.

A chemotherapy treatment known as vincristine should not be used in WM because it tends to cause peripheral neuropathy. It is, however, included in the CHOP chemotherapy regimen, which is generally reserved for the treatment of transformed disease (see page 9).

Monoclonal antibodies

Monoclonal antibodies recognize, target and stick to proteins on the surface of cancer cells. They can stimulate the body's immune system to destroy these cells.

Rituximab is used to treat B-cell lymphomas like WM. It recognizes the protein CD20, which is found on the surface of B cells. Rituximab is given by drip as an infusion directly into a vein (intravenous) or as an injection under the skin (subcutaneous).

- Rituximab may be given with chemotherapy and/or steroids and the combination then has an 'R' added (for example, bendamustine and rituximab [BR]; see below).
- It may cause allergic reactions at the time of the infusion (and afterward, but this is rare). The first infusion is given over 6 hours to try to limit this reaction. Subsequent infusions can usually be given over 60–90 minutes.
- If the starting IgM level is higher than 30 g/L, giving rituximab may result in a steep rise or flare of IgM, triggering high blood viscosity that may last for several weeks. For this reason, the rituximab may be delayed for 1 or 2 cycles of the chemotherapy schedule.

Combination treatment

Most people with symptoms will receive a combination of rituximab plus chemotherapy. The exact regimen depends on different factors, including your age and fitness. The most commonly used combinations are:

- **BR:** intravenous bendamustine on days 1 and 2 of each cycle, with rituximab also given on day 1. The treatment is repeated every 28 days (a cycle), 4–6 times.
- **DRC:** intravenous dexamethasone on day 1, intravenous rituximab on day 1, and oral cyclophosphamide twice daily for the first 5 days (days 1–5). This is repeated every 21 days (a cycle) for a total of 6 courses.

- **Single-agent rituximab:** intravenous rituximab every week, for 4 doses. This may be repeated after 3 months (called an extended schedule).
- **Other combinations** of chemotherapy agents may be used to induce a remission if you are being prepared for a stem cell transplant. Such combinations can be used to reduce the amount of WM in the body and to 'mobilize' stem cells, which can then be used for the transplant.

Proteasome inhibitors

These treatments aim to disrupt the cancer's growth and survival by targeting chemical pathways within LPL cells.

Bortezomib is given by injection under the skin (subcutaneously) every week for 4 weeks, which may or may not be followed by a week's break. It is important to highlight any symptoms of peripheral neuropathy that you have if you are taking this medication although given subcutaneously the risk is much lower than originally reported.

Carfilzomib is given by injection into a vein (intravenously). It appears to be well tolerated. It is not widely available outside clinical trials.

Ixazomib is taken by mouth (orally). It is under evaluation in combination with dexamethasone and rituximab. It is not yet available outside clinical trials.

Bruton tyrosine kinase inhibitors

These medications are designed to target and inhibit an enzyme in cells called Bruton tyrosine kinase (BTK). Blocking the effects of BTK reduces the survival of LPL cells. BTK inhibitors are taken by mouth (orally) on a daily basis for as long as they are effective and tolerated.

Ibrutinib is the first BTK inhibitor to be developed and approved for WM based on its effectiveness. It has been in clinical use for the longest time so has the longest follow-up of all the BTK inhibitors in WM. It is taken once daily in 28-day cycles. It is given for as long as it works and is tolerated. It can be used on its own or with rituximab.

Ibrutinib stops LPL cells from interacting with their surroundings so that they do not thrive. It has a number of 'off-target effects' which means that it may inadvertently adversely affect other tissues, causing side effects. These side effects include fatigue, low blood counts, disturbance of the heart rhythm (atrial fibrillation), high blood pressure, increased risk of bleeding, increased infections, aching joints, skin rashes, mouth ulcers and diarrhea. In most cases, side effects can be managed by pausing and reintroducing the treatment or reducing the dose.

You may be given additional medications to control your heart rate or blood pressure so that you can continue ibrutinib treatment. Doctors have gained a lot of experience of managing side effects that may develop over time so that you can continue your treatment.

Zanubrutinib is a 'next-generation' BTK inhibitor that has recently been approved for WM in the UK, USA and Europe. Zanubrutinib is more selective in its targeting actions in the body. It is taken twice daily as long as it is effective and tolerated.

In a head-to-head comparison trial, zanubrutinib showed a higher percentage of complete responses (CR) and very good partial responses (VGPR) (see page 35) than ibrutinib. Continued follow-up of patients in clinical trials will determine whether this higher rate of deeper responses will translate into a longer-lasting remission.

Trials have also shown that side effects such as atrial fibrillation, infections, diarrhea and high blood pressure happen less often with zanubrutinib.

Other BTK inhibitors being tested in clinical trials are acalabrutinib, tirabrutinib and pirtobrutinib.

Class effects of BTK inhibitors (side effects of all BTK inhibitors) that are important to know when using these treatments.

- **Increased risk of infections.** It is therefore common for preventative medication (prophylaxis) to be used at the same time. This typically includes an antiviral drug such as aciclovir (acyclovir in the USA) and an anti-pneumonia drug called co-trimoxazole. They are given continuously with the BTK inhibitor. If there is an additional risk of fungal infections (for example, if you are also taking steroids), then antifungal medication may also be used.
- **Increased risk of bruising and bleeding.** This means that you will need to pause your BTK inhibitor therapy for 3–5 days before any invasive procedure (such as dental extractions or operations). The exact number of days will depend on the procedure. You will be able to restart your BTK inhibitor 3–5 days after the procedure when all bleeding has stopped. Your clinical team will guide you on this.
- **Interactions with other medications and foods.** You may need to avoid certain medications or foods, or take some drugs with caution, when taking BTK inhibitors. It is important to read the information leaflet carefully and check with your clinical team about any medications, supplements or foods you should avoid.

BCL-2 inhibitors

B-cell lymphoma-2 (BCL-2) is a protein that is often overproduced in blood cancers. It can help cancer cells overcome the normal controls on growth and division. Venetoclax is an example of a BCL-2 inhibitor. It is not readily available outside of clinical trials.

Checkpoint inhibitors

Nivolumab and pembrolizumab are medications that block the effects of a protein called PD-1. They help restore the body's natural capacity to fight cancer cells. These medications are called immune checkpoint inhibitors. They are not available for the treatment of WM outside of clinical trials.

Cell therapies

When WM comes back some people may have treatment using their own stem cells. This is called autologous stem cell transplant (ASCT). Stem cells from a donor can also be transplanted. This is called allogeneic stem cell transplant (allo-SCT).

Stem cell transplants involve a specific type of stem cell called hematopoietic (blood-producing) cells, which are found in the bone marrow. All the different types of blood cell develop from these cells.

The stem cells can be collected from a donor or the person themselves – the processes are described in the next sections.

There are potentially serious side effects associated with these treatments. They are not suitable for everyone and are not done routinely. Doctors consider a person's general health and fitness before recommending them. For some people with other health problems, particularly older people, the risks of carrying out a stem cell transplant are too high to recommend this approach.

Stem cell transplants are only performed after chemotherapy. The chemotherapy puts the disease into a remission so that healthy cells can grow.

If stem cell transplant is an option, it would normally be carried out after a maximum of two previous treatments, as this is when it gives the best results.

High-dose chemotherapy and ASCT. A person having an ASCT will have some of their own stem cells collected and stored so they can be put back into their body as rescue cells after chemotherapy.

Before the cells are collected, therapy is given to reduce the number of abnormal cells in the bone marrow. This chemotherapy is typically given orally (tablets) and/or by injection and/or intravenously (into a vein) in cycles over several months.

Once the cells have been collected, high-dose chemotherapy is given to kill any remaining abnormal cells.

Then the person's stem cells are returned to the body by a drip into a vein, like a blood transfusion. The cells make their way to the bone marrow, where they form new blood cells. This takes 7–10 days. During this period, the person is particularly vulnerable to infection. Because of this, they need inpatient treatment and monitoring.

This treatment does not cure WM, but it can lead to a long-lasting remission. In other words, the disease can stay at a very low level for quite a long time (typically a number of years) before further treatment is needed.

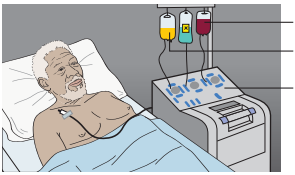
Step 1. To increase the number of stem cells and stimulate their release from the bone marrow into the blood, you will be given either:

- a drug called granulocyte-colony stimulating factor (G-CSF) plus chemotherapy about 10 days before the stem cells are collected, or
- G-CSF alone, 5–7 days before stem cell collection.

This step is called stem cell mobilization. G-CSF is a growth factor that stimulates the production of stem cells. Another treatment called plerixafor may also be given to help the stem cells become disconnected from the bone marrow and flow into the bloodstream so that more cells can be collected.

5–10 days

Step 2. Stem cell collection takes 3–4 hours. Your blood passes through an apheresis machine. Stem cells are drawn off, and the remaining blood is returned to you. Two or three sessions may be needed on consecutive days. After collection, the stem cells are frozen, placed in special bags and stored in liquid nitrogen.



1–3 days

Step 3. Conditioning therapy and stem cell reinfusion will involve a stay of 2–3 weeks in hospital. High-dose chemotherapy within 4–6 weeks of stem cell collection kills any remaining abnormal cells and prepares the bone marrow for stem cell transplantation. The stem cells that were collected are then thawed and returned to your blood via an intravenous infusion. They will travel to your bone marrow where they will settle and develop into new blood cells.

3–4 weeks

Allogeneic SCT. In this kind of transplant, the stem cells come from another person and are used as an immune therapy against the WM.

Once a donor match is secured, high-dose chemotherapy is given and the donor's previously collected stem cells are infused into the bloodstream via a cannula. Within 2–3 weeks, donor blood cells appear in the person's bone marrow.

There is an ongoing risk that the donor immune system may react against the person's healthy tissues as well as the WM cells. This is called graft-versus-host disease, and it can cause a variety of complications after the transplant.

While this form of transplant can offer the possibility of cure for some people with WM, it is more hazardous than ASCT. The risks and benefits need to be weighed very carefully.

My questions

Make a note of any questions you have about your treatment...

What are supportive treatments?

Supportive treatments are designed to counteract some of the symptoms of the disease and the side effects of treatment. In WM, supportive treatments include antibiotics to prevent infections (which may occur during chemotherapy cycles), blood transfusions, iron infusions, and plasmapheresis and intravenous immunoglobulin (IVIG).

Iron replacement

Iron is crucial for many bodily processes, including the production of red blood cells. In some people with WM, iron is not used correctly in the body. This can lead to anemia, even if there is not a large number of LPL cells in the bone marrow.

Taking iron in tablet form (oral) or in the form of a drip into the vein (intravenous) may be helpful in these circumstances. Receiving iron replacement can boost the hemoglobin and improve energy levels, delaying the need to start chemotherapy. It is important that other causes of iron deficiency (such as bleeding) are excluded first, though. Intravenous iron given once or twice a week apart is generally more effective than taking iron orally.

Blood transfusions

Your blood counts can decrease as a result of the WM itself or because chemotherapy is affecting your bone marrow as a side effect. If the counts fall to levels that cause troublesome symptoms, the medical team will consider giving you red blood cell or platelet transfusions. Transfusions are given through a cannula (a thin flexible tube) into a vein; this can be done either as a day case or as an inpatient.

Growth factors

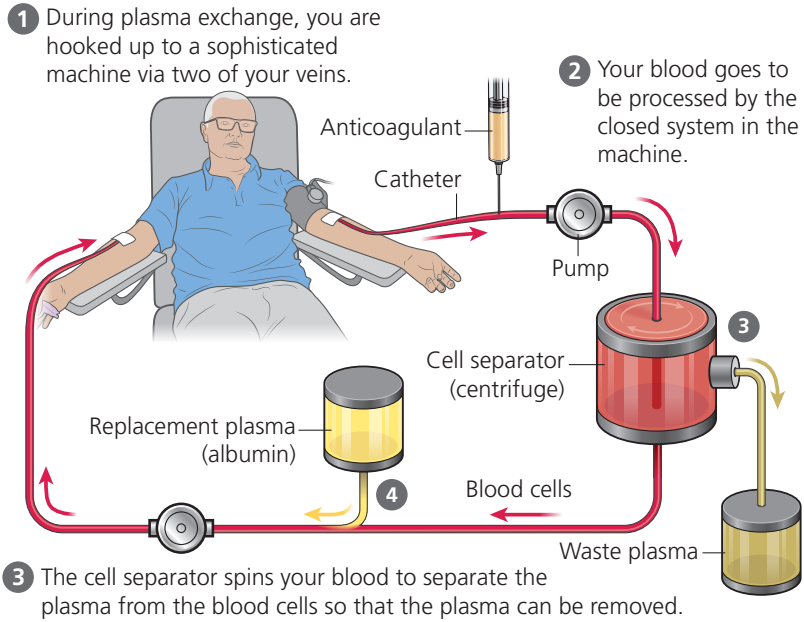
Having a low white blood cell count increases the risk of infection. White blood cells cannot be given by transfusion. Instead, growth factors can be used to boost the number of white blood cells. Growth factors are given by injection under the skin (subcutaneous) – the number of injections needed depends on individual circumstances.

Plasmapheresis or plasma exchange

Plasmapheresis can help with the effects of hyperviscosity (see page 6), which develops in up to 3 in 10 people with WM. It causes symptoms that may include nosebleeds, blurring or loss of vision, dizziness, headaches, drowsiness, poor concentration, confusion and shortness of breath.

During plasma exchange, you are hooked up to a sophisticated machine via two of your veins. Your blood leaves your body from one vein, is processed by the closed system in the machine and returned to your bloodstream through the other vein. The outpatient process typically takes 3–4 hours and is carried out in a specialist unit.

Your clinical team will work out how many plasma exchanges you need, and how often, before you start to have your main treatment.



3 The cell separator spins your blood to separate the plasma from the blood cells so that the plasma can be removed.

4 The plasma that is removed from your blood is replaced by a simple fluid containing a protein called albumin. This is mixed with your blood cells and returned to you through a vein in your other arm.

To stop the blood clotting in the machine, an anticoagulant is added at the time of the exchange. It may temporarily change the mineral balance in your body, but this is monitored and the minerals are replaced if necessary.

Prevention of infection

If you are receiving chemotherapy you may need to take medications to help prevent bacterial, viral and fungal infections as your immune system may be temporarily weakened.

This may involve taking an antibiotic, antiviral or antifungal medication. Prescribing of these varies in different centers. Sometimes a short-term antibiotic is needed, for example before an invasive dental or surgical procedure.

Vaccinations

It is important to get all the vaccines that your doctor recommends.

You should be offered pneumococcal vaccination in the form of pneumococcal conjugate vaccine followed by pneumococcal polysaccharide vaccine at least 2 months later (this is the guidance in the UK – it may differ in other countries). If you develop recurrent infections, you may benefit from a wider range of vaccines against other bacteria that cause pneumonia and meningitis.

Live vaccines against polio, herpes zoster (shingles) and yellow fever are not recommended. However, there is a non-live vaccine against herpes zoster that is approved for use in immunocompromised patients. Ask your doctor about this.

Individuals with blood cancer can be vaccinated against COVID-19 as the vaccines do not pose a risk of infection. If you are receiving chemotherapy or immunosuppression, talk to your hospital doctor about when to get vaccinated. You may respond less well to vaccines if your immune system is diminished by your WM or treatment.

Intravenous immunoglobulin

If you are less able to produce antibodies in response to infection because of your WM or your treatment, you may experience recurrent infections, such as chest infections, sinus infections or bladder infections. If you develop back-to-back infections and

require repeated courses of antibiotics or admissions to hospital, then ask your doctor to check your immunoglobulin levels.

Your immunoglobulin levels give a measure of your capacity to produce antibodies. If they are low, in particular if your IgG level is less than 4 g/L, you may benefit from IVIG infusions, which can be given monthly into a vein.

IVIG consists of antibodies extracted from blood donations that have gone through manufacturing steps to the risk of transmitting an infection.

IVIG is a precious resource that is in short supply, so your case for receiving it is likely to be assessed by a panel of experts. Certain conditions need to be met, such as vaccination against bacterial infections, as mentioned above. Once IVIG is started, its use is limited to the smallest effective dose, frequency and duration.

My questions

Make a note of any questions you have about your supportive treatments...

How do I know if treatment has worked?

If treatment is working well, your blood counts should improve and the IgM paraprotein level should fall. This is generally accompanied by an improvement in wellbeing, though you may feel some side effects from treatment.

Improvements usually happen over 4–12 weeks. You may feel better on some days than on others, but keep going with the treatment. If you feel you want to stop treatment, talk to your specialist first.

Chemotherapy is given for a fixed time period. Once an adequate response is achieved, the treatment is stopped and you will return to active monitoring.

Oral treatment, such as a BTK inhibitor, is continued as long as it is working and the side effects do not outweigh the benefits.

Response criteria

Your healthcare team may use some terms to describe how treatment is working.

Complete response or CR: the IgM paraprotein has disappeared. There is no evidence of abnormality in the bone marrow and CT scans look normal. WM symptoms have passed. A second test is needed 6 weeks later to check.

Very good partial response or VGPR: the IgM paraprotein has reduced by 90% (or more) and there are no new signs or symptoms of active disease.

Partial response or PR: the IgM paraprotein has reduced by half (or more) and abnormal swellings have reduced in size by at least half (on examination or scan). No new symptoms have developed.

Minor response or MR: the IgM paraprotein has reduced by at least one-quarter but less than one-half. No new symptoms have developed.

Stable disease or SD: the IgM paraprotein has remained stable, no new symptoms have developed and swellings have not enlarged.

Progressive disease or PD: the IgM paraprotein has increased and symptoms are worsening.

Follow-up after treatment

With current treatments, it is not possible to eradicate every abnormal cell from the body. Because of this, WM is likely to come back (relapse) at some point after treatment. All individuals need to be followed up regularly in the outpatient department, even when in remission.

The aim of follow-up appointments is to check whether the disease has returned and plan the next steps to avoid loss of wellbeing. At each follow-up visit, your doctor will take blood to check the level of IgM paraprotein and blood counts, as well as checking for symptoms and assessing your general wellbeing.

Your doctor will discuss having another bone marrow biopsy or CT scan if:

- symptoms develop – these could be the same as you had previously or they may be different ones
- the IgM paraprotein level increases for at least 2 readings, 4–6 weeks apart
- the blood counts drop.

If you have any new symptoms between appointments, contact your medical team promptly to let them know. They may want to bring your next appointment forward.

My follow-up

Make a note here of the monitoring your doctor has suggested you should have...

When WM comes back

When WM comes back, it can be treated again. The type of treatment will depend on the effects of previous treatments, how long it is since the last course of treatment and your general health. The same treatment can be used again if a year or more has passed since its initial use.

If the WM relapses more quickly than this, a different drug or a combination of drugs or a stem cell transplant might be considered.

In most people with WM, relapsed disease responds well to treatment and further remissions can be expected.

High-grade transformation

In a small number of people, WM turns into a faster-growing type of lymphoma. If this happens, it usually causes new symptoms and is detected by tests such as a lymph node biopsy. This is called transformation and, although it sounds worrying, it can be treated using more intensive chemotherapy that is normally used for high-grade lymphomas.

Active monitoring

It is very important that all treatment decisions are made with good judgment and care. A new treatment should be started for clinical reasons (symptoms) and not at the first sign that the IgM paraprotein level is rising.

The time it takes for a relapse to result in symptoms can span many months or even a few years. So, in the absence of emergency situations such as hyperviscosity, you may have a period of active monitoring that lasts a few months before treatment is started.

Research and new treatments

Clinical trials

You may be asked if you would like to take part in a clinical trial. Clinical trials are research studies that test new medical treatments or different combinations of existing treatments.

Some newer treatments are only available in a clinical trial. Not all hospitals take part in clinical trials and there may not be a trial that is suitable for you when you are diagnosed or relapse, but this is something to discuss with your specialist when planning treatment.

You do not have to take part in a clinical trial – you can always opt to have the standard treatment instead.

Studying genetic changes

Research is looking at the significance of genetic mutations such as *MYD88* and *CXCR4* mutations (see page 44) to see if medications can target them to disrupt the disease. Other genetic changes have been identified and are also being studied.

CAR T-cell therapy

You may have heard about a new type of treatment called CAR T-cell therapy (CAR stands for chimeric antigen receptor). It is currently being developed to treat different types of B-cell leukemia and lymphoma, but it is not yet a viable option for patients with WM.

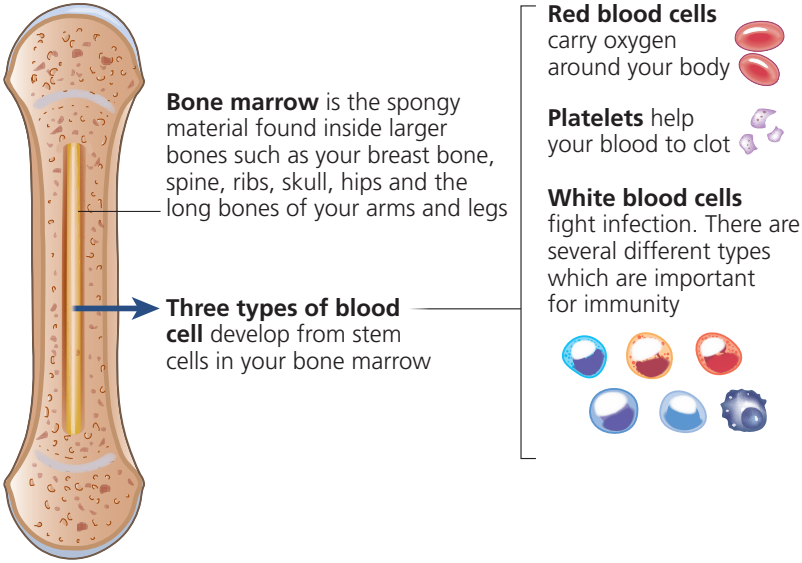
Registry data

Apart from clinical trials of new therapies, efforts are under way to capture so-called 'real-world data' using registries, which are comprehensive electronic databases with data protection measures in place. In a rare condition like WM, this kind of evidence can help researchers understand how people live with their WM, and the effects of different treatments on their WM and their lives. This information can also help healthcare funders decide on the value of treatments in the care of patients.

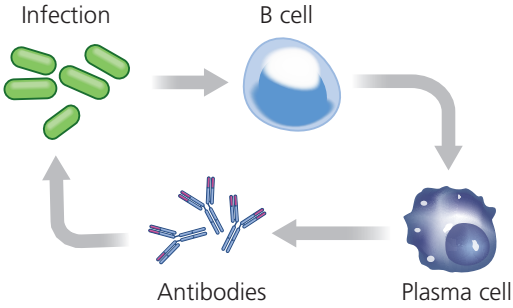
Understanding WM

To understand WM it helps to know a bit about normal blood cell production and what goes wrong.

Normal blood cell production



The cells involved in WM are a type of white blood cell called **B cells**. B cells respond to an infection by changing into plasma cells. The **plasma cells** make antibodies, which help the body to fight the infection.



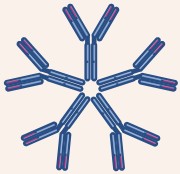
Antibodies

Antibodies are specialized Y-shaped proteins also known as immunoglobulins or gamma globulins. There are normally five types of immunoglobulin in the body: IgG, IgA, IgM, IgD and IgE. Each has a different function and size.

Usually, antibodies are made in response to infections. They help the body overcome the infection and develop immunity against future infections. IgM is the largest type of antibody because it circulates in groups of five (pentamers).

IgG

IgM



How does WM develop?

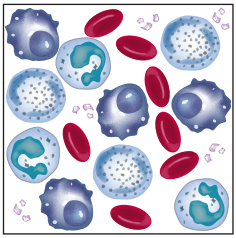
WM develops when a genetic change happens in a B cell as it is developing into a plasma cell. The change or mutation causes the cell to multiply in an uncontrolled way. The abnormal cells carrying the mutation are LPL cells.

This abnormal growth of LPL cells in the bone marrow means normal stem cells that make the different types of blood cells are crowded out. This may result in:

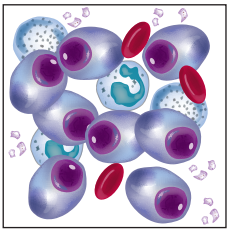
- fewer red blood cells
- fewer white blood cells
- fewer platelets

Low levels of healthy blood cells cause symptoms (see page 3).

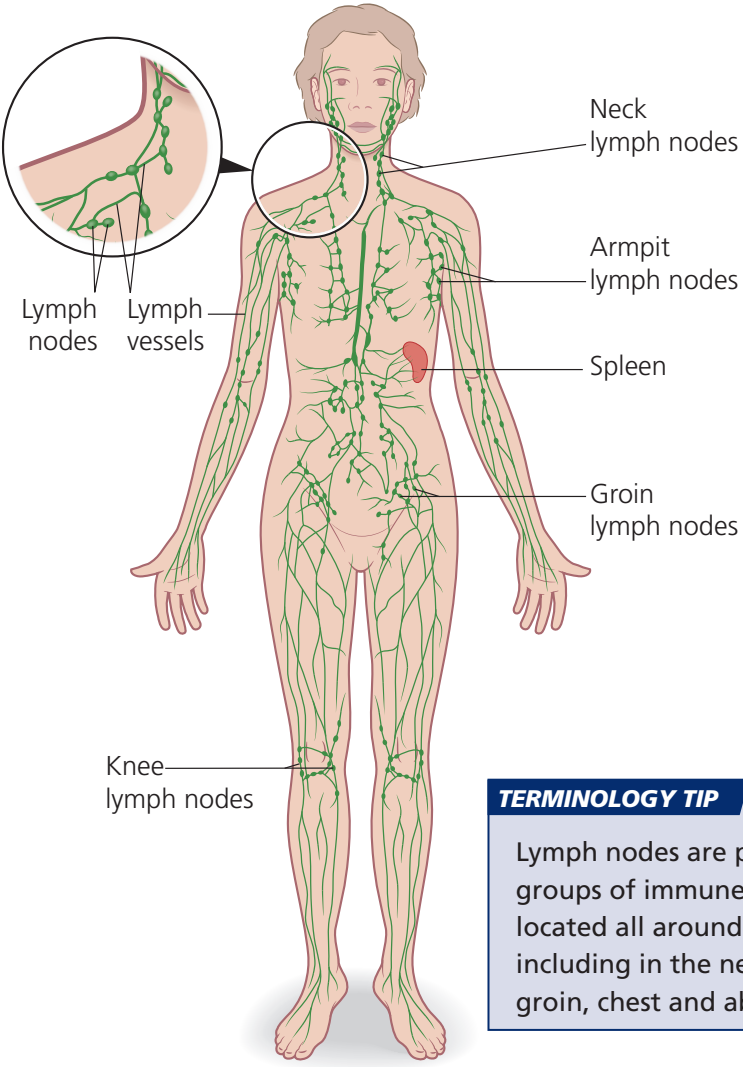
Healthy bone marrow with normal cells



Unhealthy bone marrow with LPL cells and fewer normal cells



Rarely, LPL cells also grow in the lymph nodes and other organs of the body, such as the spleen, intestine or bones. The nodes or organs may become enlarged, resulting in lumps under the skin in areas like the neck, armpit and groin or inside the body. Occasionally, the spleen enlarges enough to cause abdominal discomfort and a feeling of fullness. Sometimes, people may have changes in their bowel habit, which should be investigated. Tell your doctor if you have any unusual or persistent symptoms.



TERMINOLOGY TIP

Lymph nodes are pea-sized groups of immune system cells located all around the body, including in the neck, armpits, groin, chest and abdomen.

LPL cells are copies (clones) of one cell type (mono). So the antibodies they produce are also of one type, IgM, and are called monoclonal antibodies. IgM monoclonal antibodies (also called IgM paraproteins or M proteins) are found in the bloodstream of nearly all people with WM.

About 5% of people have non-IgM disease where the commonest paraprotein is IgG. People with this type of disease have lymphoplasmacytic lymphoma (not WM).

Jan Gosta Waldenström (1906–1996) was the Swedish doctor who first described the disease now known as Waldenström macroglobulinemia in 1944. He used the word macroglobulinemia to describe the high levels of IgM that caused notable thickness of the blood samples that he was seeing in his laboratory.

What causes WM?

Most people develop a condition called IgM monoclonal gammopathy of uncertain significance (IgM MGUS) before WM. At this early stage, there are very few LPL cells in the body, and they are often undetectable. But it is possible to detect an abnormal amount of IgM paraprotein. This may be picked up from a blood sample that has been taken for an unconnected reason. At this stage, people typically feel normal and have no symptoms.

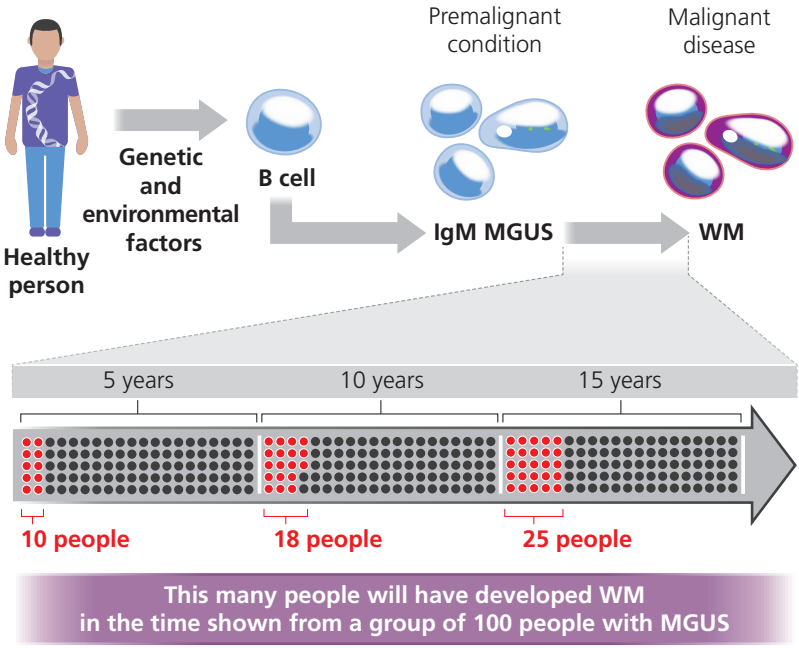
IgM MGUS becomes more common as people get older, but its cause is unknown. About 2 in 100 people aged over 50 and 3 in 100 people aged over 70 have IgM MGUS.

The raised level of IgM paraprotein in IgM MGUS usually causes no symptoms, though people are monitored once or twice a year in case the level rises or symptoms develop. Sometimes an IgM MGUS level may cause inflammation or tissue damage, which will require further tests and treatment.

Over time (usually years), the monoclonal LPL cells may build up to result in WM, which is eventually diagnosed once symptoms develop, such as fatigue, weight loss, sweats, fevers, nerve damage (peripheral neuropathy) or infections (due to an under-functioning immune system).

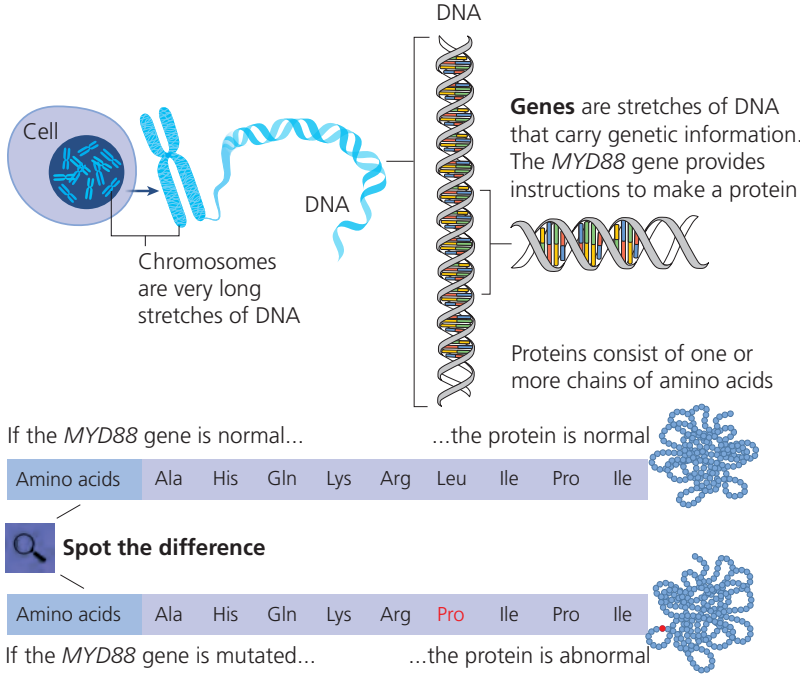
Not everyone with IgM MGUS progresses to WM. For those who do, it typically takes years.

WM is not infectious and cannot be passed on to other people. But blood relatives in the person's immediate family are slightly more likely to develop WM or another kind of B-cell lymphoma.



Genetic mutations

Most people with WM (about 90%) have a mutation in the *MYD88* gene in the DNA of the LPL cells. This mutation is not inherited from a parent. Instead, it happens inside the LPL cells. Identifying this mutation helps to confirm a diagnosis of WM and may predict how the disease will develop and respond to treatment (called the prognosis).



Changes in the *MYD88* gene's instructions change the sequence of amino acids in the protein. The amino acid leucine (Leu) is switched to proline (Pro) at position 265 in the chain. This change is called L265P.

About 40% of patients with WM have a mutation in the *CXCR4* gene, which affects production of a different protein. Mutations in the *CXCR4* gene are more varied and complicated, and therefore more difficult to analyze.

These gene mutations result in abnormal proteins that do not work properly in the body's cells.

Everyone who is suspected of having WM ideally should be tested for these gene mutations, as they may affect treatment choices.

Glossary and abbreviations

Also see Useful resources (page 16)

Anemia: a condition in which the number of red blood cells or the amount of hemoglobin in the blood is abnormally low

ASCT: autologous stem cell transplant

Beta-2-microglobulin: levels of this protein may be raised in WM

BR: bendamustine and rituximab (treatment combination)

Bruton tyrosine kinase: an enzyme that has an important role in the development of B cells

BTK: Bruton tyrosine kinase

CAD: cold agglutinin disease

Central nervous system: the brain and spinal cord

Chemoimmunotherapy: treatment with chemotherapy and immunotherapy. Chemotherapy uses drugs to kill or slow the growth of cancer cells; immunotherapy uses treatments such as monoclonal antibodies, growth factors and vaccines to stimulate or restore the ability of the immune system to fight cancer

Chemotherapy: treatment with one or more drugs that target cancer cells and other cells that divide rapidly, including cells in the bone marrow, digestive system and hair follicles

CHOP: cyclophosphamide, hydroxydaunorubicin, vincristine (or oncovin) and prednisolone (treatment combination)

CNS: central nervous system

CT: computed tomography

DLBCL: diffuse large B-cell lymphoma

DRC: dexamethasone, rituximab and cyclophosphamide (treatment combination)

Enzyme: a substance in the body – usually a protein – that helps natural chemical reactions take place

G-CSF: granulocyte-colony stimulating factor, a drug known as a growth factor. It increases the number of some types of blood cells in the blood. It can be used before and after a stem cell transplant and also with some types of chemotherapy

Gene: a section of a person's DNA that tells the body to make a specific protein

Growth factor: see G-CSF

Hyperviscosity: a condition in which the blood becomes thick

Ig: immunoglobulin

Immunotherapy: treatment that helps the immune system fight cancer or other condition

Intravenous: into a vein

IVIG: intravenous immunoglobulin

Lactate dehydrogenase (LDH): enzyme present in cells. It is involved in energy generation; when cancer is active it increases the body's energy requirements and the LDH level increases

LPL: lymphoplasmacytic lymphoma

Lymphoma: cancer affecting the lymphatic system, which includes the bone marrow, spleen, thymus, lymph nodes and lymph vessels

MAG: myelin-associated glycoprotein

MGUS: monoclonal gammopathy of uncertain significance

MR: minor response

MRI: magnetic resonance imaging

Paraprotein: an abnormal form of an immunoglobulin (antibody) that is produced in excess by a type of blood cell called a plasma cell

PET: positron emission tomography

Subcutaneous: under the skin

Viscosity: the resistance to flow. A fluid with a high viscosity is thick and sticky

WM: Waldenström macroglobulinemia

Comprehensive glossaries

iwmf.com/glossary-of-terms/

www.cancer.gov/publications/dictionaries/cancer-terms

www.macmillan.org.uk/cancer-information-and-support

My notes

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Questions for the Editor

How has this book helped you? Is there anything you didn't understand? Do you have any unanswered questions? Please send your questions, or any other comments, to fastfacts@karger.com and help readers of future editions. Thank you!

With sincere thanks to those who have reviewed this publication for all their help and guidance

HEALTHCARE

Oncology
—
Hematology

Fast Facts for Patients

Waldenström Macroglobulinemia

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