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# Lymphoplasmacytic lymphoma and Waldenström's macroglobulinaemia

Lymphoplasmacytic lymphoma is a rare non-Hodgkin lymphoma, a cancer of the lymphatic system. Nearly all lymphoplasmacytic lymphomas are the type known as 'Waldenström's macroglobulinaemia' (WM), which is named after the Swedish doctor who first described it, Jan Waldenström.

In this article we will try to answer some of the questions that people ask when they are diagnosed with this unusual condition:

- What is WM?
- Who gets WM and what causes it?
- What symptoms does it cause?
- How is WM diagnosed?
- How is WM treated and followed up?

## What is Waldenström's macroglobulinaemia?

There are over 20 different types of lymphoma, which are cancers of the lymphatic system of the body. The lymphatic system is a complex network of tubes (lymphatic vessels), glands (lymph nodes) and other organs including the spleen. It is part of the body's immune system.

Lymphomas are divided into two main types – Hodgkin lymphoma and non-Hodgkin lymphoma. Lymphoplasmacytic lymphoma (LPL) is a rare type of non-Hodgkin lymphoma. There are a few different types of LPL but Waldenström's macroglobulinaemia or WM is by far the most common kind.

Because WM is a lymphoma that usually progresses slowly over a period of months or even years, it is described as a low-grade (or indolent) non-Hodgkin lymphoma.

WM affects a blood cell called a B cell. The B cell is a type of white blood cell that is made in the bone marrow, which is spongy tissue found in the middle of many of our bones.

In fact, the bone marrow is the source of all our blood cells, including red cells (which carry oxygen), white cells (which fight infections) and platelets (which help the blood to clot).

The B cells are involved in the body's immune system. Normally, some of our B cells turn into specialised cells called 'plasma cells' whose role it is to produce proteins called 'antibodies'. Antibodies are made up of a special type of protein called an 'immunoglobulin' (shortened to 'Ig'). Antibodies help the white blood cells to fight infections and harmful substances that get into the body. There are five types of immunoglobulins formed in the body – IgA, IgD, IgE, IgG and IgM.

WM results when some B cells become cancerous and keep being made in abnormally large numbers such that they may build up in the bone marrow, the spleen and the lymph nodes (glands).

As a result of this accumulation of the lymphoma cells, large amounts of antibodies are typically produced. These particular antibodies have no useful function; in fact, some of them can have harmful effects on the body if they wrongly target the body's tissues or organs.

### **What is the difference between WM and other LPLs?**

In most people with LPL the abnormal cells produce IgM protein and the condition is then known as Waldenström's macroglobulinaemia. Compared with the other immunoglobulins, IgM forms a large molecule because it circulates in the bloodstream in groups of five and so is referred to as a 'macro' (meaning large) globulin. The term 'macroglobulinaemia' just means that there is more IgM in the blood than normal. This can result in thickening of the blood in some people.

In 1 in 20 people with LPL, either no abnormal protein is produced or the protein produced has a different identity (it might be IgG or IgA). In these cases, thickening of the blood is rare and the condition is then simply referred to as lymphoplasmacytic lymphoma rather than WM.

Despite these technical differences in the terms used, for the purposes of treatment these conditions are regarded as identical and treatment approaches are the same. So, from now on we will just refer to the condition as 'WM'.

## Who gets Waldenström's macroglobulinaemia and what causes it?

WM is a rare cancer and fewer than a hundred people are diagnosed with this type of lymphoma each year in the UK. Most people who develop WM are over 65 and it is slightly more common in men than in women. It is most common in white people.

The cause of WM is not known. Some research has shown that it might be linked in some way to hepatitis C infection or to other viral infections, but not all researchers have found these links and not everyone with WM has had one of these infections. WM itself is not infectious and cannot be passed on to other people.

WM can occur in clusters within families. A recent study of people with WM found that nearly 1 in 5 of them had a relative somewhere in the family with either WM or another similar disease. This suggests that there may be a genetic tendency for developing WM, rather than that it is directly inherited down the family line. Currently, there are no recommendations to check family members for the condition.

## Signs and symptoms of Waldenström's macroglobulinaemia

WM often develops over a long period of time and some people have no symptoms at all. This means that the condition is sometimes found by chance while you are having investigations for another condition or on a routine blood test. Most people with WM, however, gradually develop symptoms of tiredness, weakness and sometimes weight loss.

Symptoms and signs can develop due to (a) the presence of the abnormal B cells filling up the bone marrow or enlarging the lymph nodes or spleen or (b) the large amounts of IgM protein circulating in the blood.

When abnormal B cells fill up your bone marrow, it will not be able to make as many normal blood cells as usual. This can cause the following symptoms:

- tiredness, weakness and breathlessness, due to a lack of red blood cells (anaemia)
- a tendency to develop infections, due to a lack of the white blood cells that help fight infections
- a tendency to bruise or bleed easily, due to a lack of platelets.

The large amount of IgM protein in the bloodstream can make your blood thicker and more slow-flowing than normal (this is called 'hyperviscosity'). This can cause symptoms such as:

- headache
- drowsiness or confusion
- blurred vision.

The IgM protein can also affect the nerves to the hands and feet and this can cause symptoms of weakness, tingling or numbness, usually in the fingers or toes.

Some people with WM develop poor circulation in the hands and feet, especially when it is cold. If you notice this symptom you should mention it to your doctor because you might need to have a special blood test to look for a substance called a cryoglobulin.

Unlike people with other types of non-Hodgkin lymphoma, people with WM do not often have swelling of their lymph glands or spleen.

## **What tests might I have?**

Your doctor will ask about your symptoms and general health, and will do a full physical examination. If the doctor suspects that you have hyperviscosity you will have an eye examination to look at the back of your eyes with a light. This is because the blood vessels at the back of the eyes can become enlarged or leaky due to the high levels of IgM protein in the bloodstream.

### **Blood tests**

The main test that is used to identify this type of lymphoma is a simple blood test that measures the IgM protein level. The IgM level is usually raised in WM. Other immunoglobulin protein levels (eg IgA and IgG levels) are sometimes low and it is thought that this might be the reason why some people are prone to sinus and bronchial infections when they have WM. A simple blood sample will also show if the levels of red blood cells, white blood cells or platelets are low.

### **Bone marrow biopsy**

A sample of your bone marrow (a biopsy) may be taken to look for abnormal B cells. This is done on a ward or in the outpatients department and takes about 15–20 minutes. Before the biopsy an injection of local anaesthetic is given into the skin over the hip bone. A small sample is taken from the hip bone using a needle and sent to the laboratory.

This can be an uncomfortable procedure to have done but the local anaesthetic numbs the area, making it less painful.

The bone marrow sample is looked at under a microscope to see what types of cells are present and how many there are. The cells will also be examined using a special technique called immunophenotyping. The result takes 7–10 days to come back.

### **Other tests**

Computed tomography (CT) scans, ultrasound scans and lymph node biopsies might also be necessary in order to assess whether your lymph nodes, liver or spleen are affected. This gives the doctors an idea of how extensive the lymphoma is within the body, so that decisions can be made about whether or when to start treatment.

If you would like more information on CT scans or on ultrasound, please ask the helpline for our information sheets on these investigations.

## **How is Waldenström's macroglobulinaemia treated?**

If you have been diagnosed with WM you might have no treatment at all for a while (see below) or you might have one or more of the following treatments:

- chemotherapy drugs
- steroids
- monoclonal antibodies
- stem cell transplant.

You might also need other treatments if you have thickening of your blood, if your blood counts are low, or if you have side effects from the chemotherapy drugs. These additional treatments are called 'supportive' treatments.

The treatment you will be given will depend on your particular circumstances. It will depend on the results of all the tests, on your symptoms and on your age and general health.

### **'Watch and wait'**

Because WM develops slowly, sometimes with no symptoms at all, some people will not need any treatment at the beginning and some people will never require treatment.

As we described earlier, your WM might even have been diagnosed when you were having tests for something else altogether.

If the doctor decides that no treatment is needed, you will have regular check-ups to assess how you are feeling and to take blood tests to measure the blood cell counts and the IgM levels. This kind of follow-up with check-ups but without treatment is quite common in people with non-Hodgkin lymphoma and is sometimes called a 'watch and wait' approach.

Even though this approach is only taken because it is in your best interests medically, 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 relative good health. If you would like to talk about watch and wait, please telephone our helpline.

### **When does treatment start?**

You are usually started on treatment for WM if one or more of the following occur:

- you develop symptoms of WM (see above) or your symptoms become more troublesome
- your blood IgM levels increase
- your blood cell counts change (eg when the red blood cell count or platelet count fall).

Although WM is not a curable disease, it is very treatable and many people live with this disease for many years. Treatment is aimed at improving your quality of life and keeping you well for as long as possible, with the least possible side effects.

### **Chemotherapy**

Chemotherapy (treatment with anti-cancer drugs) can be given to destroy the abnormal B cells. Several chemotherapy drugs have been proved to be effective in WM. Some of these drugs are given intravenously (into a vein through a plastic tube called a cannula), some are taken by mouth in tablet or liquid form, and some are given subcutaneously (injected just under the skin).

When treating WM, two or more drugs with different actions may be used together. These drug combinations are more effective than single drugs in attacking the abnormal B cells. The drugs are given in cycles over a period of a few months, meaning that you will have treatment some weeks but not others. This allows healthy blood and bone marrow cells to recover between treatments.

There are a number of different combinations and doses of drugs used. Your treatment will be specially and individually tailored by your medical team, to ensure that you are having the best and most suitable course of treatment for you. Which drug or drug

combination is chosen will depend on your age, what symptoms you have, how severe your symptoms are and your blood counts. It will also depend on what treatments you might possibly require in the future (certain drugs are best avoided, for example, if you might need a stem cell transplant later on).

The different chemotherapy treatments commonly used to treat WM are described below.

**Chlorambucil:** Chlorambucil is a commonly used chemotherapy drug and is taken in tablet form. It is usually taken daily for a period of time specified by the doctor. Its side effects are normally mild.

**Fludarabine and cladribine:** Fludarabine can be given as tablets or intravenously, usually every day for 5 days. Treatment is usually repeated every 3–4 weeks for 6–8 months. This chemotherapy produces a more rapid response than chlorambucil, but its side effects can be more severe.

Cladribine is a similar type of drug to fludarabine and has similar side effects, but it is given using a different schedule. It can be given intravenously or subcutaneously every 6–8 weeks for two courses.

**Other chemotherapy drugs:** Other types of chemotherapy drugs such as cyclophosphamide, doxorubicin and vincristine may be used in certain situations. These drugs are typically given in combinations known as ‘CHOP’ or ‘CVP’, in which the ‘P’ stands for prednisolone, a type of steroid that is given at the same time as the chemotherapy drugs (see below). These combinations are usually given every 3 weeks for six cycles.

Other combinations of chemotherapy drugs and other agents may also be used – your medical team will discuss these with you.

### Potential side effects of chemotherapy

All chemotherapy drugs have potential side effects. These vary from patient to patient and the different drugs used. It is important to remember that most side effects are manageable, however, and will resolve once treatment is finished.

Common side effects of chemotherapy include nausea, loss of appetite, change in bowel habit, hair thinning or loss, and an increased tendency to develop infections, bruising and bleeding.

## **Steroids**

Steroids are used to reduce inflammation in many medical conditions. In WM they also appear to cause a process called 'programmed cell death'. This means that steroids can trigger the destruction of the abnormal B cells. When used in combination with chemotherapy, steroids can make your lymphoma more responsive to the chemotherapy drugs and therefore make the treatment more effective.

In the treatment of WM, steroids are usually given by mouth in tablet or liquid form, but they can also be given intravenously.

## **Potential side effects of steroids**

Side effects of steroids do vary. It is important to remember that each person's reaction to steroids can be different and that side effects, if any, are temporary and should resolve when the steroids are stopped. Common side effects of steroids include indigestion, increased blood sugar, increased blood pressure, increased risk of infection, increased appetite, mood changes and weakness due to muscle wasting.

## **Monoclonal antibody treatment**

Monoclonal antibodies are drugs that recognise, target, and stick to certain proteins on the surface of some cancer cells. This marks out the cells for destruction by the body's immune system. A monoclonal antibody called rituximab is sometimes used in the treatment of WM, alongside chemotherapy and/or steroid treatment.

Rituximab is given slowly into your vein the first time it is given and then it is given a bit more quickly on subsequent infusions if it is well tolerated.

## **Potential side effects of monoclonal antibodies**

You can experience flushes, sweats, a fast pulse rate and a decrease in blood pressure during the infusion of rituximab, which is why the first infusion is given slowly.

Most people tolerate this drug without problems, however.

## **Less commonly used drugs and new drugs**

Other drugs that have been shown to be effective in clinical trials, either alone or combined with other drugs, include bortezomib, bendamustine, thalidomide and ofatumumab. Although effective, these drugs are still being tested in clinical trials and are not yet in general use. Permission to use these drugs usually needs to be specifically sought from the regulatory bodies by the doctor before they can be used. New drugs are becoming available all the time and continue to be tested in clinical trials.

If you would like more information on chemotherapy drugs, steroids or rituximab or on the side effects of these treatments, we have a number of information sheets available – please ask the helpline for these.

### **Stem cell transplantation**

This is also known as ‘peripheral blood stem cell transplantation’. Stem cell transplants are sometimes considered for people with WM who are fit enough to tolerate the intensity of this type of treatment. Stem cells can be obtained either from your own blood or from a donor and they are infused (dripped slowly through a cannula into your vein) after you have had a course of high-dose chemotherapy.

**Autologous stem cell transplant:** When you act as your own donor, this is known as an ‘autologous’ transplant. In this form of transplant your own stem cells are collected. Having the cells collected is a bit like what happens when you give blood. These cells are stored until after you have had your course of high-dose chemotherapy to kill any remaining lymphoma cells. Your stem cells are then returned to you. They make their way to your bone marrow, where they form new blood cells to restore your bone marrow to normal function.

This form of stem cell transplant is not curative, but it can lead to you having a long-lasting remission, meaning that the disease can stay at a very low level for quite a long time before further treatment is needed.

**Allogeneic stem cell transplant:** When the stem cells come from another person this is known as an ‘allogeneic’ transplant. The donor might be a brother or sister or someone not related to you but whose tissue type matches yours. In this type of stem cell transplant, the donor’s stem cells produce donor blood cells in the your bone marrow, and these cells can directly fight against any leftover lymphoma cells so that the disease is treated using the donor’s immune system as the weapon.

While this form of transplant can offer the possibility of cure for some people with WM, it is a more hazardous procedure than an autologous transplant and your general health has to be good before you would be considered for it. You would need to think about the risks and benefits very carefully before embarking on this form of treatment. Your medical team would discuss this option in detail with you if they felt you could benefit from it.

We have booklets on these two types of stem cell transplant. Please ask the helpline if you would like a copy of one or both of these.

## Supportive treatments

Supportive treatments are designed to counteract some of the symptoms of the lymphoma and the side effects of the treatments. In WM, these supportive treatments include blood transfusions, antibiotics that are given to prevent infections (usually when you are receiving chemotherapy), and plasmapheresis.

**Blood transfusions:** As we have seen, your red cell or platelet 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 significant symptoms (such as tiredness, light-headedness or breathlessness due to anaemia or easy bruising or bleeding due to low platelets), the medical team will consider giving you red cell or platelet transfusions. Transfusions are given through a cannula into the vein and this can be done either as a day case or as an inpatient.

**Plasmapheresis:** If the IgM protein in your blood is causing symptoms, especially if it is causing heart problems, the blood can be thinned by a procedure called plasmapheresis (sometimes called plasma exchange). This takes 1–3 hours.

In this procedure a cannula is placed into a vein in each arm. Blood is slowly removed from one arm and the blood is passed through a special machine that separates the liquid part of the blood, the 'plasma' (which contains the IgM protein) from the blood cells. The blood cells are then put back, together with an artificial plasma substitute, into the other arm. This might only need to be done once, before the chemotherapy has taken effect for example, but it might have to be done several times.

## Follow-up

Because WM is a low-grade non-Hodgkin lymphoma which you can have for many years and which is very likely to relapse at some point after treatment, you will need to be followed up regularly in the outpatient department.

At each visit, you will have blood tests taken to check the level of the IgM protein and your blood counts to make sure that the WM is stable. If there is a change in circumstances, such as new symptoms or a rise in the IgM protein or a fall in the blood counts, you might have another bone marrow biopsy or CT scan to reassess your condition.

If you develop any new symptoms between appointments you should make contact with your medical team to discuss the symptoms. If necessary your next appointment could then be brought forward.

When the WM comes back the same treatment can be used again if a year or more has passed since the initial treatment. If the WM relapses more quickly than this, a different drug or a combination of drugs or a stem cell transplant might be considered.

### **Research and clinical trials**

You might be asked if you would like to take part in a clinical trial. These are research studies that test new medical treatments. Clinical trials are very important in improving future treatments for people with your type of lymphoma.

Not all hospitals take part in clinical trials and there might not be a trial that is recruiting people with WM when you are diagnosed, but this is something that you might like to discuss with your specialist when planning treatment. You do not have to take part in a clinical trial and can always opt to have the standard treatment instead.

### **Acknowledgement**

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### **Further resources**

#### **International Waldenström's Macroglobulinaemia Foundation**

[www.iwmf.com](http://www.iwmf.com)

An international charity that provides information and support for people with Waldenström's macroglobulinaemia.

#### **WMUK**

UK point of contact for people with WM and annual WM seminar.

Email: [info@wmuk.org.uk](mailto:info@wmuk.org.uk)

[www.wmuk.org.uk](http://www.wmuk.org.uk)

UK support group: Nigel Pardoe and Cheryl Luckie

Email: [info@wmsupportgroup.org.uk](mailto:info@wmsupportgroup.org.uk)

☎ 020 8326 3286

[www.wmsupportgroup.org.uk](http://www.wmsupportgroup.org.uk)

#### **Macmillan Cancer Support**

☎ Free helpline: 0808 808 00 00

[www.macmillan.org.uk](http://www.macmillan.org.uk)



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Our publications are written by experienced medical writers, in close collaboration with medical advisers with expertise in the appropriate field. Textbooks and professional journals are consulted to ensure that information is as up to date as possible. References are provided where they have been used. Some publications are written by professionals themselves, acting on guidance provided by the Lymphoma Association. Our publications are reviewed every two years and updated as necessary.

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