

Waldenström's Macroglobulinaemia & Lymphoplasmacytic lymphoma

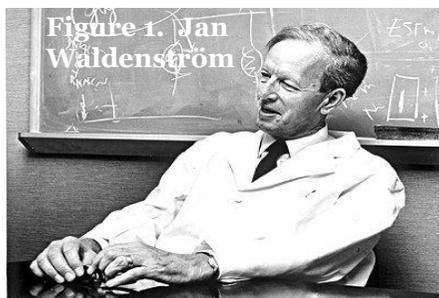
What is WM?

Non-Hodgkin lymphoma (“NHL”) is a cancer of the lymphatic system and lymphoplasmacytic lymphoma (“LPL”) is a rare type of NHL.

Jan Waldenström was the Swedish doctor who first described the disease now

known as Waldenström's macroglobulinaemia (“WM”) in 1944 and “macroglobulinaemia” was the word he used to describe the high levels of IgM “**paraprotein**” (meaning an abnormal version of the usually normal IgM protein) seen in the blood stream of 95% of patients with LPL. WM is the term describing LPL characterised by production of IgM paraprotein.

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 when needed). The blood cells made in the bone marrow are continuously released from the bone marrow into the bloodstream. The lymphatic system is part of the body's immune system and helps us fight infection, and consists of organs such as the bone marrow, thymus, spleen, and the lymph nodes (or lymph glands). Lymph nodes are connected by a network of tiny lymphatic vessels that contain lymph fluid and are found in groups, particularly in the armpits, the neck



and the groin. Some groups of lymph nodes are situated more deeply, in the chest and abdomen. There is also lymphatic tissue in other organs, such as the skin, lungs and stomach.

B-cells are a type of white blood cell that develop into “plasma cells”, which in turn make antibodies to help fight infections. Antibodies are made from a special type of protein called “immunoglobulin” and there are 5 types of immunoglobulins (Ig) in the body: IgG, IgA, IgM, IgD and IgE. Each of these antibodies has a different function and size. Usually, antibodies are made in response to infections in order to help the body fight against them and so develop immunity. IgM is the largest of these, as it circulates in groups of five. WM affects B cells when they are in the process of developing into plasma cells. These developing cells are called “lymphoplasmacytic cells”, because they have features of both lymphocytes and plasma cells, which is where the name “lymphoplasmacytic lymphoma” comes from.

In WM, the bone marrow produces abnormal lymphoplasmacytic cells. Although they are of no use to the body, these cells keep being made. As their numbers increase, they build up within the bone marrow, lymph nodes, spleen and other organs. In the bone marrow the result of this build-up is that the normal blood cells are ‘crowded out’ and this leads to a gradual reduction of normal blood counts. If the build-up occurs in the lymph nodes, spleen or even elsewhere, these tissues swell up and lumps sometimes form that can be visible or felt, although this is not as common a finding as in other lymphomas.

What is the difference between WM and LPL?

In most people with LPL the abnormal B cells produce IgM protein and the condition is then known as “Waldenström’s macroglobulinaemia”. The term ‘macroglobulinaemia’ just means that there is more of the large (or **macro**) IgM type of immunoglobulin in the blood (**‘aemia’**) than normal.

The B cells that build up in large numbers when someone has an LPL often produce large amounts of antibody. Unlike the antibodies we produce when we have an infection, however, the antibodies produced by the B cells in LPL have no useful function. In fact, some of them can have harmful effects on the body if they wrongly target the body’s own tissues or organs.

Large amounts of IgM in the blood can cause it to become thicker than normal. This is known as “hyperviscosity”. Sometimes, the IgM (being an antibody) may wrongly recognise the body’s tissues as foreign and attach on to them causing damage or inflammation. This may result in damage to nerves (‘neuropathy’) or destruction of blood cells (‘autoimmune haemolytic anaemia’).

In around 1 in 20 people with an LPL, there is no abnormal immunoglobulin protein produced, or the abnormal B cells produce a different immunoglobulin type (IgG or IgA types, for example). When there is no immunoglobulin produced or the smaller immunoglobulins are produced, the condition is known simply as ‘lymphoplasmacytic lymphoma’ rather than WM and thickening of the blood does not occur. Despite these technical differences in terminology, the tests and treatments for these

conditions are the same. So, from now on we will just refer to all LPL in this article as ‘WM’.

Causes of Waldenström’s macroglobulinaemia

The causes of WM are unknown. Like other cancers, it is not infectious and cannot be passed on to other people. There does seem to be a familial tendency to have WM or other kind of lymphoma in immediate blood (“1st-degree”) relatives of WM patients. This tendency is between 5 and 20 times more common than in the normal population but is not enough to warrant screening of family members.

In most cases, WM is preceded by a condition known as “**monoclonal gammopathy of uncertain significance**” (“**MGUS**”) which is how WM itself is thought to start. At this the very early stage, there are very few LPL cells in the body (often undetectable even if a biopsy is attempted) but there is a detectable amount of abnormal IgM (usually a low level). This may be picked up on a blood sample done for an unconnected reason, and at this stage people are typically feeling normal and have no symptoms. The cause of MGUS (and hence WM) is not known, but it is commoner as people get older. About 1 in 50 people over the age of 50 years of age have MGUS. For the vast majority of people, this protein has no implications, other than to need monitoring once or twice a year in case it rises. In a small proportion of people, the protein may result in harmful effects in the body, such as inflammation or damage of tissues such as blood cells or nerves. In such people, further evaluation is needed and treatment is sometimes given to limit the damage caused by the protein.

Over time (usually years), monoclonal cells may gradually build up and accumulate. If they accumulate enough to affect the functioning of the body, symptoms such as fatigue, weight loss, sweats, fevers or infections (due to an under functioning immune system) may develop and WM is eventually diagnosed.

MGUS and WM are at the opposite ends of a spectrum that moves forwards over time. The rate of progression is variable and typically spans many years. The number of persons progressing from MGUS to WM builds up

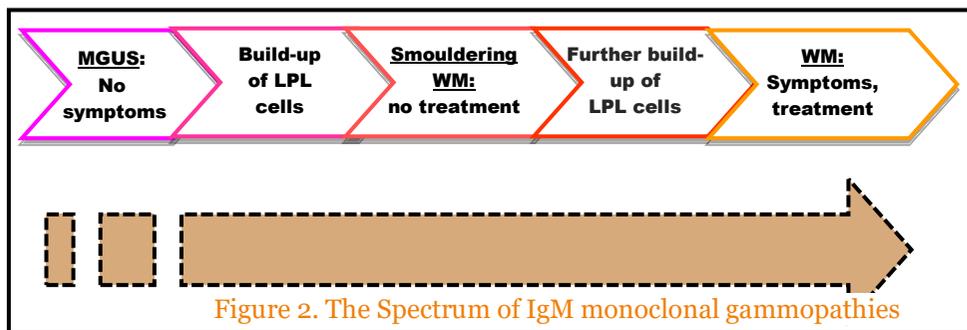


Figure 2. The Spectrum of IgM monoclonal gammopathies

over time. By 5 years, 10% progress; by 10 years, 18% progress and by 15 years nearly a quarter progress to WM.

The symptoms of Waldenström’s macroglobulinaemia

WM often develops over a long period of time (many years) and many people have no symptoms at all. This means that the condition is sometimes found by chance while having investigations for another condition or on a routine blood test. About a quarter of people with WM are diagnosed by chance like this. Most people with WM, however, gradually develop symptoms due to the disease. Symptoms develop for two main reasons. The first is that abnormal cells fill up the bone marrow or collect in the lymph nodes or the spleen (and, rarely, in other places in the body). The second

reason for developing symptoms in WM is the presence of large amounts of IgM protein circulating in the blood.

Symptoms caused by a build-up of lymphoma cells

When abnormal B cells accumulate and fill up the bone marrow, it is not able to make as many normal blood cells as usual. This can cause:

- 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.

If lymph nodes enlarge you might notice swollen glands and if the spleen is swollen this can be uncomfortable or painful.

People with WM may experience fevers, night sweats and weight loss. These are symptoms that are a particular feature of lymphomas and you might hear them referred to as “**B symptoms**”. They reflect the additional metabolic activity (the production and use of energy) of the LPL cells in the body. If such symptoms become marked, such as to require (for example) a change of nightclothes on a regular basis or significant weight loss, they should be mentioned to the doctor and may indicate the need for treatment. While all these symptoms can also be caused by other conditions, they should always be checked out by a doctor.

Rarely, WM lymphoma cells can build up in other parts of the body, forming masses or tumours. These can occur almost anywhere in the body - they have been described in the spine, limbs, lungs, around the eye socket

and palate, in the gut and the skin. These masses are usually slow-growing but they can cause symptoms if they press on surrounding organs, nerves or blood vessels. Very rarely, people may experience symptoms affecting the central nervous system, such as fits, weakness of the facial muscles, double vision. These symptoms may be a sign of the WM affecting the brain and are called “**Bing-Neel Syndrome**”. Special tests such as brain scans and sampling of the spinal fluid (a lumbar puncture) are needed to identify these cells. This is a very rare complication of WM, which can be treated if recognised promptly but requires special treatments.

Symptoms caused by the IgM protein

If there is a large amount of IgM protein in the bloodstream this can make your blood thicker and more slow-flowing than normal. This is called **hyperviscosity**. Hyperviscosity develops in up to 30% of people with WM.

This can cause symptoms such as:

- nosebleeds
- blurring or loss of vision
- dizziness or headaches
- drowsiness, poor concentration or confusion
- shortness of breath due to heart failure or lung congestion.

Hyperviscosity can cause changes in the back of the eyes (the retinas) due to pressure in the retinal blood vessels. These changes can be seen readily by a hand-held instrument called an ophthalmoscope, which is found in GP surgeries, opticians and hospital outpatients. It provides a simple tool for assessing whether the hyperviscosity needs to be treated urgently (if there is bleeding in the back of the eyes). A blood test called **plasma or serum**

viscosity can be done to measure the degree of thickness of the blood, but it is not available in all hospitals. If the plasma viscosity test is high, then a special procedure known as plasma exchange may be recommended. This can only be done in certain hospitals. Also, treatment for the underlying lymphoma needs to be started to get to the root of the problem.

Sometimes people develop numbness or tingling in their hands and feet, or problems with their balance. This may be due to nerve damage in the extremities (“**peripheral neuropathy**”) caused by the abnormal IgM which damages the nerves (axons) or their insulating structures (myelin) . It is important to mention such symptoms to the doctor, especially if they are getting worse over time. It may be necessary to carry out special tests to examine the nervous system in more detail, for example: a scan of the brain or spinal cord, a lumbar puncture to look for signs of inflammation in the spinal fluid, nerve conduction studies to see how well the nerves are conducting electrical impulses or even a nerve biopsy (a procedure done under a local anaesthetic).

In some people with WM the IgM has a tendency to cause the red blood cells to stick together in the 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, especially when it is cold, which may cause colour changes or breakdown of the skin in these areas. 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 protein called a **cryoglobulin**. This protein can also cause damage to nerves by inflaming their blood supply (vasculitis) or other

organs such as the kidneys. If such problems are present, treatment for the underlying lymphoma may be needed.

In some patients, the antibody properties of the IgM may cause the red cells to clump together in the cooler parts of the body (the fingers, toes) and be broken apart by the immune system resulting in so-called **Cold Agglutinin Disease (CAD)**. This can result in a sudden fall in haemoglobin (anaemia) with symptoms such as fatigue and shortness of breath and the presence of dark brown urine due to the spill over of red cell pigment (haemoglobin) in the urine (haemoglobinuria). This may occur in the setting of MGUS or WM and needs prompt treatment. A transfusion of blood may be needed in the short term. Treatment of the underlying lymphoma is usually recommended when this happens. There are also new treatments that can suppress the breakdown of red blood cells called complement antibodies being assessed in clinical trials (see later section).

Diagnosis of Waldenström's macroglobulinaemia

Your doctor will ask about your symptoms and general health, and will carry out a full physical examination. If the doctor suspects that you have hyperviscosity you will need blood tests, a bone marrow biopsy and scans to quantify the WM and treatment is likely to be commenced urgently.

Testing for IgM

Blood consists of blood cells (red blood cells, white blood cells and platelets), floating in a liquid called "plasma", which contains a vast array of proteins with different functions. When a blood sample is taken, it is collected in one of several types of blood tubes. Some tubes have an additive

to prevent the blood from clotting so that the blood cells can be analysed (e.g. a blood count); others have an additive that is designed to clot the blood cells, so removing all the clotting factors which bind the blood cells together, leaving just serum (which contains the remaining proteins, including immunoglobulins). Finally, some tubes contain additives which prevent clotting of the blood; the tube is spun so that the cells are separated from the rest of the plasma and analysis is carried out on the plasma itself (e.g. to check the clotting system).

In WM, the excessive amount of IgM is measured by a technique called "serum protein electrophoresis" (SPE). This test is carried out on patient's serum and separates all proteins in the blood according to their electrical charge by running an electric current through the serum sample, either in a tube or in a gel.

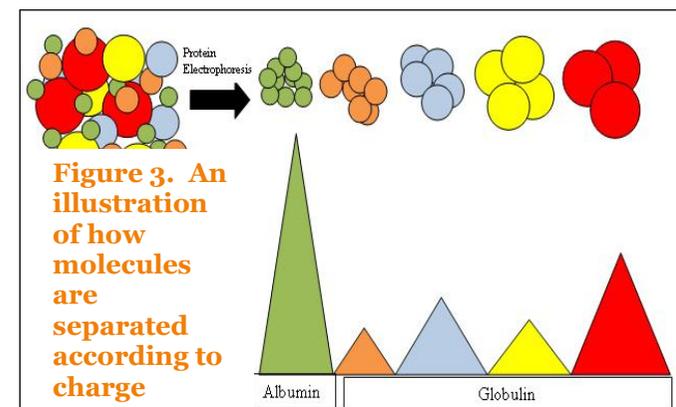


Figure 4. The tracing obtained from normal serum showing a low and broad-based gamma (γ) region

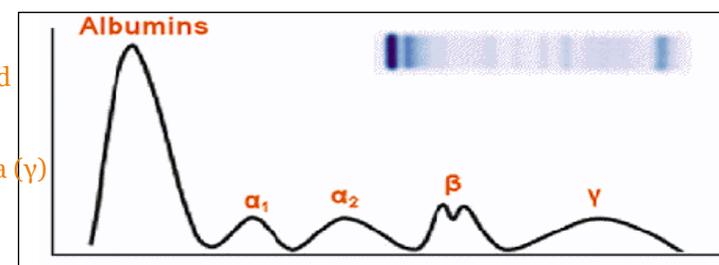
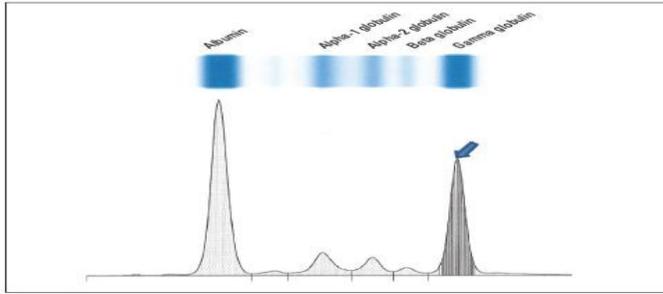


Figure 5. An 'M' or monoclonal spike (blue arrow) is present in WM in the gamma region



As IgM is such a large molecule, it is often difficult to measure the amount of protein accurately. The higher the level, the less likely it is that the result will be accurate. Some laboratories just report the total IgM level (in other words, the abnormal IgM resulting from WM as well as normal IgM that is still present), while others report the M-protein or 'paraprotein', which is the abnormal IgM on its own. It does not really matter which method is used, as long as it is consistently applied when following up an individual patient.

Other immunoglobulin levels (e.g. of IgA and IgG) are sometimes low and it is thought that this might be the reason why some people with WM are prone to sinus and bronchial infections.

A simple blood sample will show if the levels of red blood cells, white blood cells or platelets are low. Your blood tests will also show how well your liver and kidneys are functioning.

Bone marrow biopsy



Figure 6. The position adopted by the patient for bone marrow biopsy

Since WM is a disease of the bone marrow, it is essential to sample the marrow in order to confirm that LPL cells are present, how plentiful they are, and how much normally functioning bone marrow is remaining. This procedure is called "bone marrow biopsy" (BMB). The samples are usually taken from the back of your hip bone (pelvis). You will be given an injection of local anaesthetic 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 (a trephine biopsy). Both samples will then be looked at under a microscope.

A BMB can be done on the ward or in the outpatients department and no prior fasting is required. The whole procedure takes about 15-20 minutes. It may be uncomfortable as the liquid marrow is drawn into the syringe or as the bone biopsy is taken with a needle, but any discomfort should only last for a few seconds. A small dressing or plaster is placed on the skin after the procedure and you will be free to move around straight afterwards. Sedation for BMB is no longer recommended due to the risk involved, but some centres offer 'Entonox' or gas-and-air to breathe while having the procedure done.

You may feel bruised and have an ache for a few

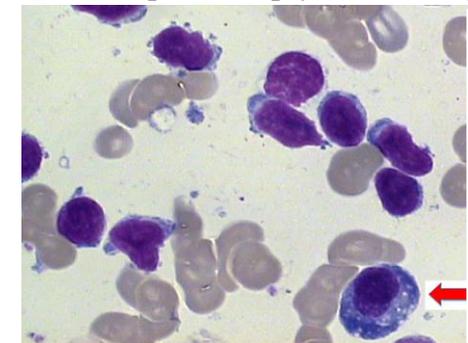


Figure 7. Bone marrow sample. A normal B plasma cell is marked, the rest are mainly WM cells.



days after the test, but this can be eased with mild painkillers if necessary. The results of the BMB usually take around 7 to 10 days to come through because of the processing involved.

Increasingly, new ways of analysing the bone marrow in more detail are becoming available, including some genetic tests that are carried out on the LPL cells. Genetic abnormalities called MYD88 and CXCR4 mutations are under investigation by researchers. In some hospitals, a test is now carried out on the bone marrow to see if these abnormalities are present. Their precise significance in terms of prognosis and treatment is still the subject of concentrated research. There is emerging evidence that the presence or absence of these mutations can affect the behaviour of the WM and its response to treatments. However, it is too early to base specific recommendations on the information we have so far. It is important for further trials to be done.

Scans

CT (computed tomography) scan

A CT scan is a special type of x-ray. It is used to find out if WM has affected lymph nodes, or organs such as the liver or spleen. A number of pictures are taken from different angles and fed into a computer which shows detailed pictures of the inside of the body. The process involves lying still for 30-45 minutes. You may be asked not to eat or drink anything for at

least four hours before your appointment. Most people who have a CT scan are given a drink beforehand or an injection into a vein in the arm at the time of the scan. This injection of a substance called “contrast” allows particular areas of the

inside of the body to be seen more clearly and may make you feel hot all over for a few minutes afterwards. If you have kidney problems, the use of contrast should be avoided as this can make the kidneys worse.

PET-CT (Positron Emission Tomography) - CT scan

A PET-CT scan is a body scan in which an injection of labelled glucose is injected in to the vein and a scan performed to see whether the labelled glucose is taken up by the body’s tissues. Such uptake occurs when the tissues are actively metabolising. This kind of scan—which involves more x-rays than a CT scan—does not usually add further information in the setting of WM, unless there is a suspicion that the condition is behaving more aggressively than before.

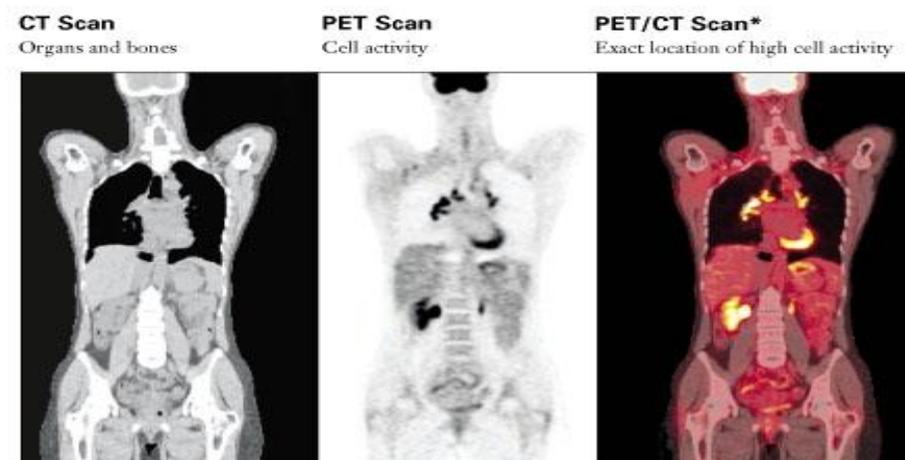


Figure 8. A patient being prepared for a CT scan

How is Waldenström's macroglobulinaemia treated?

Although WM is not curable, it is very treatable and most people live with this disease for many years. Some people who are diagnosed with WM do not need any treatment at first. WM often develops slowly over years and the term often used to describe this gradual behaviour is '**indolent**'. This means that some people may not need treatment for months or, very often, years. If this is the approach your doctor recommends you will have regular check-ups in the outpatients' clinic. This active monitoring is often called 'watch and wait' or 'watchful waiting' (see below).

Watch and wait

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 your blood cell counts and IgM levels. This kind of follow-up, with check-ups but without treatment, is quite common in people with a low-grade non-Hodgkin lymphoma. If you have no symptoms of WM you will typically be seen in the clinic every 3–6 months for clinical review and blood tests.

The watch and wait approach is followed because it is in your best interests medically, as there is no evidence that earlier intervention is advantageous. Nevertheless, 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 this happens, it is important to share this with your clinical team and family and friends, so that you can work out a way to cope.

When does treatment start?

Your doctor will consider starting treatment if:

- you begin to get increasing symptoms attributable to WM
- the level of IgM protein in your blood is increasing or hyperviscosity develops
- your blood count changes, such as developing low levels of red blood cells (anaemia)
- you develop complications such as a progressive neuropathy, cryoglobulinaemia or cold agglutinin disease that is felt to be due to the effects of the abnormal IgM

The treatment you will be given will depend on your particular circumstances and the medical team will prescribe the most suitable drugs for you on the basis of:

- the results of all the tests
- your symptoms – for example how severe they are and whether or not you have neuropathy
- your age and general health.

Treatment is aimed at improving your quality of life and keeping you well for as long as possible, with the least possible side effects. The main treatment for WM has for many years been chemotherapy. However as a result of research and clinical trials, many novel therapies are becoming available to treat WM patients – these are the so-called “biological therapies”. Other treatments such as blood transfusions, growth factor injections or plasma exchange may also be used to improve particular symptoms. These additional treatments are called ‘supportive treatments’.

If your doctor thinks that you need treatment, you might have one or more of these treatments:

- **chemotherapy drugs**
- **steroids**
- **monoclonal antibodies**
- **biological treatments**
- **stem cell transplant.**

Chemotherapy

Chemotherapy (chemo) is the use of anti-cancer (cytotoxic) drugs to destroy cancer cells, and can be given: as tablets; into a vein ('intravenously'); or as an injection under the skin ('subcutaneously'). You may be given just one type of chemotherapy drug or you may be given two or more such drugs together (combination chemotherapy). The selection of treatment is determined by the nature of the problems you are facing as a result of your WM and your own state of health, which will impact on your ability to tolerate different treatments. Some treatments can affect the stem cells in your bone marrow and should be avoided if there is a chance of needing a stem cell transplant in the future (see section on stem cell transplants for what this involves). You may be offered the chance to participate in a clinical trial.

Your specialist will explain which treatment is appropriate for you, but if ever you feel unsure of what is being offered or why, you can consider seeking 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 to follow.

If you are treated with just one chemotherapy drug, any side effects are likely to be mild. If you are having treatment with a combination of drugs you may have more side effects. However most treatments for WM are given in outpatients and do not require admission to hospital unless complications such as infections occur. Your doctor or specialist nurse can tell you what to expect. You should always tell them about any side effects you have and ask them questions about your concerns. Very effective medicines are available to reduce side effects if necessary. Treatment for WM usually spans 4 to 6 months. Sometimes the condition seems to be slow to respond but patience is important as a response is forthcoming in most cases, 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, fevers, shivering or shaking so it can be treated straight away. The chemotherapy drugs most commonly used to treat WM are listed below.

Chlorambucil (Leukeran®)

Chlorambucil is taken as a tablet and is usually given for 7 to 10 consecutive days per month for the time recommended by your specialist. It should be kept in the fridge. It may be given with a steroid called prednisolone and with the monoclonal antibody, rituximab (see later section). Treatment is given monthly for 6 months. Chlorambucil should be avoided in anyone in

whom a stem cell transplant is being considered as it damages stem cells and makes it difficult to collect them later.

Fludarabine (Fludara ®)

Fludarabine is usually taken as tablets, but it may be given as a ‘drip’ into a vein (intravenous infusion) for up to 5 days per month. It may be given with other agents such as cyclophosphamide and rituximab. Usually 6 months of treatment are required. Fludarabine should be avoided in anyone in whom a stem cell transplant may be considered in the future as it damages stem cells and makes it difficult to collect them later.

Cladribine (Leustat ®)

Cladribine is a similar type of drug to fludarabine. It may be given as a ‘drip’ into a vein (intravenous infusion) or as an injection just under the skin (subcutaneous injection). It may be given with other agents such as rituximab. Each treatment cycle consists of 5 daily doses of cladribine as a subcutaneous injection, plus 4 weekly intravenous infusions of rituximab. This is typically repeated just once after 2 or 3 months of a rest period. Cladribine should be avoided in anyone in whom a stem cell transplant is being considered as it damages stem cells and makes it difficult to collect them later.

Cyclophosphamide

Cyclophosphamide may be taken as tablets or given into a vein (intravenously). It is usually given in combination with other agents, such as in the DRC regimen, which consists also of dexamethasone (a steroid), rituximab, or the CHOP regimen, which is made up of cyclophosphamide, hydroxydaunorubicin, vincristine (or oncovin), and prednisolone. These

regimens are not toxic to stem cells and can be used even if a transplant is planned in the future.

Bendamustine (Levact ®)

Bendamustine is given as a ‘drip’ into a vein. It is usually given on day 1 and 2 of a 4-week cycle in combination with rituximab, which is given only on day 1 of the cycle. Although not currently approved by the National Institute for Health and Care Excellence (NICE), bendamustine is available and funded through the government-backed National Cancer Drugs Fund. Bendamustine can be used safely in patients who may need a stem cell transplant in the future.

Steroids

Steroids are often used as part of the treatment as they can help the other drugs to destroy the abnormal B-cells and make chemotherapy more effective. They're usually given as tablets, but may also be given as an injection into a vein (intravenously). Steroids are usually given for 1 to 5 days per month depending on the chemotherapy schedule. The side effects of steroids—including fluid retention, weight gain, restlessness, agitation and sleep disturbance, a tendency to high blood sugar and high blood pressure—are temporary and usually go away when treatment finishes.

Monoclonal antibody therapy

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

A monoclonal antibody called Rituximab is used to treat B cell lymphomas like WM. It targets the protein CD20 found on B-lymphocytes and is given

as a drip into a vein (infusion). Rituximab may be given with chemotherapy and/or steroids and the combination then has an 'R' added (i.e. R-CHOP). It may cause allergic reactions at the time of the infusion (and rarely afterwards) and the first infusion is given over 6 hours to try and limit this reaction. Subsequent infusions can usually be given over 90 minutes.

Ofatumumab (Arzerra®) and obinutuzumab (GA101)

Ofatumumab (Arzerra®) and obinutuzumab (GA101) are newer anti-CD20 monoclonal antibodies that also appear effective in indolent lymphomas including WM. Ofatumumab is sometimes used instead of Rituximab when the reaction to Rituximab is too extreme to continue.

Biological therapies

A great deal of international collaboration and effort in recent years means that there are novel therapies becoming available for patients with WM. This includes agents which target chemical pathways within the LPL cells and also affect the way LPL cells collaborate with the environment in which they live (the bone marrow microenvironment). Such agents include bortezomib (Velcade®), carfilzomib (Kyprolis®), Ixazomib (Ninlaro®), ibrutinib (Imbruvica®), acalabrutinib (ACP-196), venetoclax (Venclexta®) and idelalisib (Zydelig®). Others include the so-called immunomodulatory drugs that are related to thalidomide, including lenalidomide (Revlimid®) and pomalidomide (Imnovid®).

Bortezomib (Velcade®)

Bortezomib is a 'proteasome inhibitor' and appears to kill LPL cells as well as hamper their support networks within the bone marrow. It has shown encouraging results in trials and appears to be especially effective at

lowering a high level of IgM and may also be useful in the setting of high blood viscosity. It is given subcutaneously either twice a week for 2 weeks and then a week's break; or weekly for 4 weeks followed by a week's break. At present, Bortezomib is not available in the NHS in England for patients with WM.

The main side effects of bortezomib are tingling, numbness or pain in the hands and feet, but this seems to be less of a problem now that it is given subcutaneously. It is important to highlight any symptoms of peripheral neuropathy that are present at the outset, in order that that a close eye is kept to avoid worsening of this problem with the use of Velcade.

Carfilzomib (Kyprolis®)

Carfilzomib is a 'next-generation' proteasome inhibitor related to bortezomib that is given intravenously. It has been analysed in conjunction with rituximab and dexamethasone in 31 patients with WM, of whom nearly 90% were previously untreated. The overall response rate in this trial was 81%, with 65% achieving more than a partial response. It was well tolerated and, after 9 months, two-thirds of the patients treated remain stable. Studies are ongoing in the US, and it is not yet possible to prescribe carfilzomib for WM outside of a trial.

Ixazomib (Ninlaro®)

Ixazomib is an orally administered proteasome inhibitor which has recently been evaluated in WM in combination with dexamethasone and Rituximab and showed an impressive overall response rate that was close to 90% in previously untreated patients. Importantly there was no sign of nerve damage. It is not yet available outside of a trial.

Ibrutinib (Imbruvica®)

Ibrutinib is an investigational agent designed to specifically target and inhibit a signaling protein in cells called Bruton's tyrosine kinase (BTK). BTK is a key mediator of B-cell survival, meaning that, through multiple signaling systems within cells, BTK regulation helps to direct malignant B-cells to lymphoid tissues, thus allowing such abnormal cells access to a special environment that encourages their survival. As mentioned previously, more than 90% of patients with WM have the MYD88 mutation, which is intimately connected to BTK. Through deactivation of BTK, ibrutinib has been found to abolish binding of MYD88 to BTK in MYD88-expressing WM cells.

Another mutation has been identified that seems to provide further insight into which patients are more likely to respond to ibrutinib. The C-X-C chemokine receptor type 4 (CXCR4) plays a crucial role in modulating the biology of B-cell lymphoproliferative disorders (see section on Future Directions for more information).

The pivotal study was done at the Dana Farber Cancer Institute by Steven Treon and colleagues, who treated 63 patients with relapsed or refractory WM with ibrutinib for up to 2 years. Two-thirds of patients showed a partial response or better.

Ibrutinib comes in the form of a 140 mg strength tablet in Europe which requires 3 tablets to be taken daily, unless the dose has been reduced by the treating doctor. Recently, a 420 mg tablet was introduced in the USA but there are no imminent plans to do the same in Europe.

The USA's Food and Drug Administration (FDA) granted ibrutinib 'Breakthrough Therapy Designation' for use as a single agent in previously treated or resistant WM and is licensed in Europe by the European Medicines Agency, and became available on the Cancer Drugs Fund in October 2017 for people with relapsed or refractory WM. The CDF status of Ibrutinib will be reviewed by the National Institute for Care Excellence in late 2019; UK access to Ibrutinib might change at this point.

Acalabrutinib (ACP-196)

An orally available second generation inhibitor of Bruton's tyrosine kinase (BTK) which prevents the activation of the B-cell antigen receptor (BCR) signaling pathway. This leads to an inhibition of the growth of malignant B cells that overexpress BTK such as WM cells. A trial of Acalabrutinib in WM was completed in 2016 in the UK and elsewhere and patients remain under follow up. In the disease, CLL, this drug has been shown to be highly effective and able to overcome resistance to Ibrutinib in some cases. It is not currently possible to prescribe Acalabrutinib outside of trials.

Zanubrutinib (BGB3111)

BGB-3111 is a potent and highly selective small molecule BTK inhibitor (Bruton's Tyrosine Kinase), being developed for the treatment of a variety of lymphomas including WM. A global, randomized Phase III trial of BGB-3111 in patients with WM designed to determine whether the quality of response with BGB-3111 in WM is superior to that of ibrutinib was launched globally in 2017 and close to completing recruitment as of June 2018. One of the

questions that this trial will address is the effectiveness of Zanubrutinib in patients without the MYD88 mutation.

Tirabrutinib

ONO/GS-4059 (tirabrutinib) is a highly potent and selective BTK inhibitor which is also being explored in clinical trials. Tirabrutinib forms a specific connection with a target in the BTK molecule and, like ibrutinib, irreversibly inhibits its activity.

Idelalisib (Zydelig®)

Idelalisib is another investigational drug, also a tablet. Idelalisib targets the phosphoinositide 3-kinase (PI3K) delta (PI3K) pathway, which is activated in patients with the MYD88 mutation. Signalling in cells by this PI3K delta pathway is critical for the growth, development, survival and movement of B lymphocytes and is overactive in many B-cell lymphomas including WM. Idelalisib acts by blocking this pathway and is being developed both as a single agent and in combination with approved and investigational therapies. Recently, a Phase II study evaluating the safety and efficacy of idelalisib in patients with relapsed and/or refractory symptomatic WM was prematurely closed owing to the high incidence of liver damage.

Thalidomide (Thalomid®) and Lenalidomide (Revlimid®)

Thalidomide and lenalidomide are two related drugs, known as ‘immunomodulatory drugs’. Both have been trialed in WM patients with limited success, due to problematic side effects that were noted (peripheral nerve damage in the case of thalidomide and marked anaemia in the case of

lenalidomide). These difficulties, as well as the advent of other, newer, agents, have led to a cessation of trials of these agents at this time.

Pomalidomide (Imnovid®)

Pomalidomide is a third-generation immunomodulatory drug. Pomalidomide can stop cancer cells from growing abnormally and may also stimulate the immune system to fight the cancer cells and possibly improve the effectiveness of the steroid dexamethasone and the monoclonal antibody rituximab to fight WM cells. This drug, which is taken in tablet form, has been used experimentally in a related condition called multiple myeloma and information from these other research studies suggests that pomalidomide may help to reduce or prevent the growth of cancer cells. Clinical trials are underway which show promising results in WM without the kind of side effects noted with thalidomide and lenalidomide.

Checkpoint inhibitors Nivolumab (Opdivo®) and Pembrolizumab (Keytruda®)

Programmed cell death protein 1, also known as PD-1 and CD279, is a cell surface receptor that plays an important role in controlling the immune system. This protein is expressed on malignant B-cells in WM and signalling through PD-1 may promote WM cell growth and survival. By counteracting PD-1, Nivolumab and Pembrolizumab restore the body’s capacity to activate the anti-tumour response and fight cancer cells. See later section of upcoming trials for a planned study of Pembrolizumab in combination with Rituximab.

Venetoclax (ABT-199/GDC-0199)

B-cell lymphoma-2 (BCL-2) is a protein that is commonly overexpressed in hematologic malignancies, enabling cancer cells to escape so-called programmed cell death. BCL-2 overexpression is also associated with tumor development, disease progression, and drug resistance. Venetoclax is a potent, highly selective, orally bioavailable small molecule that binds to and inhibits overexpressed BCL-2. It has been trialed in a variety of B cell lymphomas including a small number of patients with WM and shown to produce decent response rates with an acceptable safety profile.

Stem cell transplantation

Some people with WM may have treatment involving the use of their own stem cells (autologous stem cell transplant, ASCT) or stem cells from a donor (allogeneic stem cell transplant, allo-SCT). Stem cells (in this context a specific type of stem cells called 'haematopoietic cells' or 'HPCs', i.e. "blood-producing cells") are cells found in the bone marrow that can give rise to all categories of blood cells. In health, they keep the bone marrow populated to account for the natural turnover of our cells. They are found in the bone marrow and can be collected from the patient or donor before high dose chemotherapy is given to the patient and can be returned afterwards to help the marrow to become repopulated once again. ASCT is sometimes called "high-dose chemotherapy with stem cell rescue".

There are serious side effects associated with these treatments. They are not suitable for everyone and are not done routinely. Doctors take into account a person's general health and fitness before recommending them. This often

means that the risks of carrying out stem cell transplants in older persons who have other health problems are too high to recommend this approach. Stem cell transplants are only performed after chemotherapy has been given to reduce the burden of the disease and put it into a remission and serve to consolidate (build on) that remission. If considered, it is recommended that stem cell transplants are carried out after one or two lines of previous treatment, as this is when the results are best.

Autologous stem cell transplant

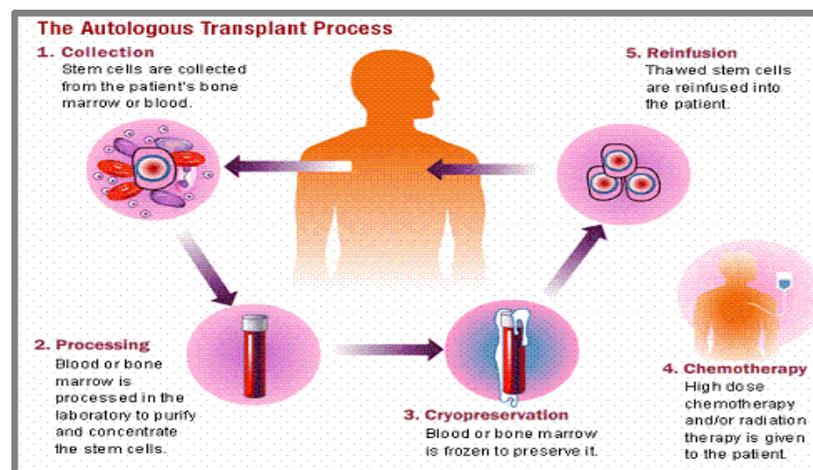


Figure 10. A schema showing the steps involved in autologous stem cell transplantation

Patients due to undergo ASCT have some of their own stem cells collected and stored in advance of receiving a course of high-dose chemotherapy to kill any remaining lymphoma cells. A combination known as LEAM is often used (this stands for Lomustine, Etoposide, Ara-C and Melphalan), administered over a 5 day period intravenously. Once returned to the body (dripped in to the vein like a blood transfusion), the stem cells make their

way to the bone marrow, where they form new blood cells to restore the bone marrow to normal function. While the stem cells are making their way to the bone marrow and becoming re-established there, the patient is particularly vulnerable to infection and requires a period of inpatient treatment and monitoring. This form of stem cell transplant is not curative, 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.

Allogeneic stem cell transplant

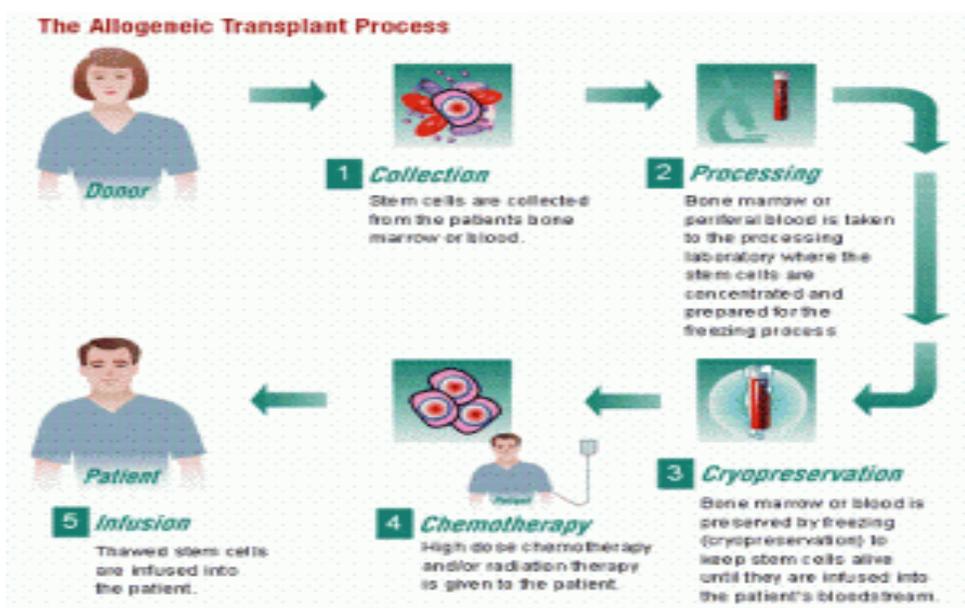


Figure 11. The steps involved in obtaining donor stem cells and their eventual use in the patient

In this kind of transplant the stem cells come from another person. The donor might be close relative, such as a brother or sister, or may be someone unrelated who has a matching tissue type. After the patient receives high dose chemotherapy, the donor's stem cells are infused into the

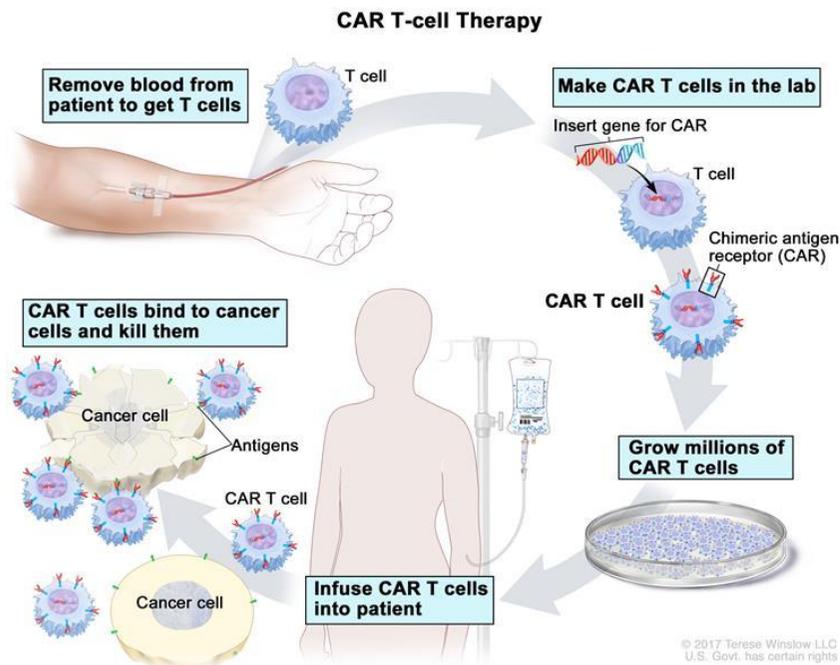
bloodstream via a cannula and within 2 or 3 weeks, produce donor blood cells in the patient's bone marrow. These new cells resupply the patient with blood cells which can also directly fight against any leftover lymphoma cells. In this kind of stem cell transplant, the donor's immune system is used as the weapon within the patient. There is an ongoing risk that the donor immune system may react against the patient's healthy tissues as well

(graft-versus host disease), causing a variety of complications after the transplant. Special treatment is needed to suppress the patient's immune system for a period of time to allow it to accept the donor's cells (even though they are a tissue match), and this inevitably leads to the risk of unusual and dangerous infections. As with ASCT, a period of hospitalisation is inevitable.

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 the patient's general health has to be good before you would be considered for it. The risks and benefits need to be weighed very carefully before embarking on this form of treatment.

CAR T-cell therapy (chimeric antigen receptor T-cell therapy)

A type of treatment in which a patient's T cells (a type of immune system cell) are changed in the laboratory so they will attack cancer cells. T cells are taken from a patient's blood. Then the gene for a special receptor that binds to a certain protein on the patient's cancer cells is added in the laboratory. The special receptor is called a chimeric antigen receptor (CAR). Large numbers of the CAR T cells are grown in the laboratory and given to the patient by infusion. CAR T-cell therapy is being studied in the treatment of some types of cancer. Also called chimeric antigen receptor T-cell therapy.



CAR therapy can cause prolonged toxicities because the engineered T-cells can persist in the body even after treatment is no longer required. This may result in elevated levels of chemicals known as cytokines that can lead to the so-called 'cytokine release syndrome' or CRS in severe cases by the immune system that is associated with dangerously low blood pressure and a marked reaction syndrome, in which the entire body becomes inflamed. These immune reactions are usually treated with steroids or neutralizing antibodies, but can be fatal in some cases. Neurologic toxic effects have also been reported, including confusion, hallucinations, and seizures. There are also complications associated with depletion of healthy cells that also express the target antigen and risk of infections.

CAR engineering is still being perfected, and once optimised through further clinical trials, will offer an attractive treatment approach for B-cell malignancies. It can be used as a conduit to stem cell transplantation or as a solo potentially curative therapy for relapsed/refractory diseases. By ensuring the proper connection of active agents to effector T-cells, CAR therapy bypasses several potential points of resistance in relapsed/refractory diseases.

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 antibiotics that are given to prevent infections (which may occur during chemotherapy cycles), blood transfusions and plasmapheresis.

Blood transfusions 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 troublesome



Figure 12. 2 bags of packed red cells being transfused in to the patient

symptoms, the medical team will consider giving you red cell or platelet transfusions. Transfusions are given through a cannula (a thin flexible tube) into the vein and this can be done either as a day case or as an inpatient. If you have to have several blood transfusions over time, your blood will need to be checked regularly to check the cell counts and ferritin level. The ferritin level is an indication of your body's store of iron and it is important that this doesn't get too high. White blood cells cannot be given by transfusion; rather growth factor injections can be used to boost the white blood count if it is low and increasing the risk of infection.

Plasma Exchange



Figure 13. A typical apheresis (cell separator) machine used both for plasma exchange and peripheral blood stem cell harvesting

If the IgM protein in the blood is causing symptoms, especially if it is causing heart or breathing problems, the blood can be thinned by a procedure called 'plasmapheresis'. This is alternatively called 'plasma exchange' and it 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 passed 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.

Taking part in a clinical research trial

You might be asked if you would like to take part in a clinical trial, a research study that tests new medical treatments. Clinical trials are very important in improving future treatments for people with your type of lymphoma. Also, some of the newer treatments are only available for people who are taking part in trials.

Not all hospitals take part in clinical trials and there might not be a trial that is suitable for you 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.

Upcoming trials in the UK

RAINBOW (up-front)

Following on from the very successful R2W study, this trial looks at the incorporation of ibrutinib into frontline therapy for this disease. The lead investigator for this study is Dr Rebecca Auer (St Bartholomew's Hospital, London) but it will be open at several centres across the UK, hopefully in the autumn/winter of 2018. There are 2 objectives: (1) to assess the toxicity and effectiveness of the 'chemotherapy-free' combination of Rituximab and Ibrutinib (RI) as primary therapy for WM, and (2) to assess whether

progression-free survival is improved with Rituximab/Ibrutinib when compared to Dexamethasone/ Rituximab/ cyclophosphamide (DRC).

Pembro WM (relapse)

This study, a phase II trial to investigate the safety and effectiveness of Rituximab and Pembrolizumab in relapsed/refractory WM is led by Dr Jaimal Kothari (Oxford) and will be opened across the UK hopefully later this year.

Cardinal and Cadenza Studies for Cold Agglutinin Disease (CAD)

These are 2 studies opening in 3 centres in the UK this year: UCLH (Dr Shirley D'Sa), Leeds (Dr Anita Hill) and Bournemouth (Dr Helen McCarthy) for patients with troublesome cold agglutinin disease resulting in anaemia or thrombosis due to so-called 'cold haemolysis' that may or may not require transfusions. The treatment consists of infusions of an antibody treatment that targets part of the immune system called the 'complement system' which is instrumental in cold haemolysis.

How will I be followed up?

WM is an indolent lymphoma that patients can have for many years. With current therapies it is not possible to eradicate every last abnormal cell from the body and thus WM is very likely to relapse at some point after treatment. Consequently, all patients need to be followed up regularly in the outpatient department even when in remission, so as to detect a return of the disease and plan the next steps in a timely way so as to avoid a significant fall in wellbeing.

At each visit, blood tests are taken to check the level of the IgM protein and the blood counts to make sure that the WM is stable. If new symptoms develop—the same ones at diagnosis or new ones—or if there is a rise in the IgM protein or a fall in the blood counts, another bone marrow biopsy or CT scan will be advised to reassess the disease status.

In addition any new symptoms that arise between appointments should prompt contact with your medical team to discuss the symptoms. If necessary the next appointment could be brought forward.

What happens when WM comes back?

When the WM comes back it can be treated again. The treatment will depend on how well prior treatments have been tolerated, how long it is since the last course of treatment and your state of 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 more advantageous.

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

Future directions

Recently identified genetic abnormalities found in patients with WM are being further explored to examine their significance for prognosis and treatment. The MYD88 mutation is found in more than 90% of patients

with WM and in up to 80% of persons with IgM MGUS. It predicts for progression from IgM MGUS to WM, but its significance in WM is still being analysed.

In nearly one-third of patients with WM this specific genetic mutation in the CXCR4 gene is present and, in experiments with laboratory cell samples ('cell lines'), the researchers found that WM tumour cells with the CXCR4 mutation proliferated more quickly than those without the mutation. It is hypothesised that the CXCR4 mutation drives the disease, in other words that it spurs WM cells to grow, divide, and spread.

As previously mentioned, there are a large number of novel therapies being tested in WM with promising results.

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2018- Review June 2019



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