FACT SHEET

Waldenstrom's Macroglobulinemia (WM)

OVERVIEW

Lymphoma is the 6th most common cancer in Australia in adult men and women. It can affect people of all ages and is the most common blood cancer. Lymphoma is a cancer of the immune system and affects lymphocytes - a type of white blood cell. When lymphocytes gain DNA mutations they divide and grow uncontrollably resulting in lymphoma.

There are two main types of lymphocytes - B-cells and T-cells. Lymphomas growing from B-cells are more common and account for around 85% of lymphoma cases; those caused by T-cells around 15%. The first lymphoma to be discovered was called "Hodgkin lymphoma" (HL - around 15% of all B-cell lymphomas), after Thomas Hodgkin, who described it. All subsequent lymphomas discovered were called "non-Hodgkin lymphoma" (NHL around 90% of all lymphomas, both B and T-cell lymphomas).

There are over 80 different subtypes of lymphoma, which can be classified according to how fast they grow. "Aggressive" (or high-grade) lymphomas are those that grow quickly, usually weeks to months and need treatment immediately. "Indolent" (or low-grade) lymphomas usually develop over months to years and often are not treated straight away but are monitored. It is important to know your subtype of lymphoma. Lymphoma cells can travel to any part of the body and be found in lymph nodes, the bone marrow, the spleen, blood, bone, skin and almost any organ or tissue.

WALDENSTROM'S MACROGLOBULINEMIA

Waldenström's macroglobulinemia (WM) is a very rare subtype of B-cell lymphoma, comprising only 2% of people with lymphoma. WM is considered to be an indolent (slow growing) lymphoma that usually affects older adults and is primarily found in the bone marrow although lymph nodes and spleen may also be involved.

WM is treatable with available therapies in the majority of patients but is not curable. The abnormal WM cells grow mainly in the bone marrow and as a result, the normal healthy cells produced in the bone marrow can be low in number leading to complications within the body. As a result, the red cells that carry oxygen, the white cells that fight infection and the platelets that help with blood clotting can be crowded out and normal blood cell production is disrupted.

Low levels of red cells can lead to anaemia making people feel tired and weak, low numbers of white cells make it hard for the body to fight infections and a low platelet count can result in increased risk of bleeding and bruising. At the time of diagnosis, WM most commonly involves the bone marrow and blood, however WM can start almost anywhere in the body and spread to lymph nodes, spleen, stomach, intestines or lungs. WM very rarely involves the skin and thyroid gland.

WM causes the overproduction of a monoclonal protein called "immunoglobulin M" referred to as IgM, that can result in a thickening of blood known as hyper-viscosity which causes the blood to thicken and impairs blood flow. These IgM immunoglobulins help the body fight infection and low levels of normal.

DIANOSIS AND STAGING

A biopsy is not always required for a diagnosis of WM. A biopsy is a surgical procedure to remove part of or all of an affected lymph node or other abnormal tissue to look at it under the microscope although most commonly the biopsy tissue for a diagnosis of WM comes from the bone marrow or a blood test.

Once a diagnosis of WM is made, there are further tests that need to be performed to see where else in the body the lymphoma may be and is referred to as staging. Because WM is a blood cancer the lymphoma can travel all over the body, so it is important that a check of the entire body is done looking for the lymphoma. Staging tests may include:

- Bone marrow biopsy
- Blood tests to check for IgM level and low blood counts
- Urine tests to check for IgM level
- Positron emission tomography (PET) /CT scan
- Computed tomography (CT) scan
- Baseline tests prior to treatment to check organ function that may include; heart scan, kidney scan, and blood tests

SIGNS AND SMPTOMS

At least 25% of patients with WM are asymptomatic (have

no symptoms) and the lymphoma is diagnosed because of abnormal blood counts from general blood test that has been ordered. Many asymptomatic patients do not require treatment although some patients that are symptomatic (have symptoms) may start treatment soon after diagnosis. Some patients have hyper-viscosity syndrome (although uncommon) as mentioned above and some symptoms of this can include;

- Abnormal bleeding especially from the nose, gums and lining of the gastrointestinal tract
- Fatigue
- Shortness of breath
- Headache
- Recurrent infections
- Peripheral neuropathy
- Muscle cramps
- Changes in metal status

TREATMENT OPTIONS

Although WM is an incurable lymphoma, it is very treatable, and patients generally have a long-term response to treatments. Some patients with WM who do not have any symptoms at diagnosis may not be treated for many years. In these cases, the patient is monitored closely in an approach known as 'watch and wait'. Treatment is only started once the IgM protein is too high and symptoms are present. To date there is no evidence to suggest that starting a treatment on a patient with WM who has no symptoms provides a greater survival benefit to those who continue on the 'watch and wait' approach. See "Understanding Watch & Wait" fact sheet on the website.

If treatment is needed, the patient's type and severity of the symptoms, age, overall health and degree of thickness of the blood, will help determine which treatment is selected. Treatment regimens may be a combination of chemotherapy and monoclonal antibody agents, that may include:

- Bendamustine and rituximab (BR)
- Rituximab, cyclophosphamide (oral) and dexamethasone (DRC)
- Rituximab and ibrutinib (BTK inhibitor)
- Ibrutinib only – if unsuitable for chemo-immunotherapy
- Clinical trial

In rare cases, patients with WM who have hyper-viscosity syndrome may need to undergo a procedure called a plasma exchange to temporarily reverse and prevent symptoms prior to treatment commencing. The plasma exchange involves the use of an apheresis machine to remove the patient's blood through a line from the veins to pass it through the machine, separate the plasma from the rest if the blood, exchange it with donated plasma that does not contain the IgM protein and return this to the patient. This is a very effective treatment but will only have temporary effects on the WM which is why other treatments are required.

For patients whose WM relapses the next treatment utilised depends upon the time the WM has been under control and all the other factors considered initially as stated above.

- > 5 years years since last treatment can repeat original treatment
- 2 years or less since initial treatment, a different treatment
- Rituximab and chemotherapy
- Ibrutinib (BTK inhibitor)
- Clinical trial

TREATMENTS UNDER INVESTIGATION

Many new individual and combination medicines are currently being tested in clinical trials around the world for both newly diagnosed and relapsed or refractory WM including:

- Idelalisib (Zydelig™)
- Ofatumumab (Arzerra™)
- Bortezomib (Velcade™)
- Lenalidomide (Revlimid™)
- Obinutuzumab (Gazyva™)
- Venetoclax (Venclexta™)
- Zanubrutinib (Brukinsa™)
- Acalabrutinib (Calquence™)
- Chimeric Antigen Receptor (CAR) T-cell Therapy

CLINICAL TRIALS

Clinical trials are essential in identifying effective medicines and determining optimal doses of these medicines for people diagnosed with lymphoma. Patients who are interested in participating in a clinical trial can find one using the following methods:

1. Speak to their specialist to see what options are available
2. See 'Understanding Clinical Trials' fact sheet on the website for websites to find a clinical trial.

RESOURCES AND SUPPORT

Organisation	How can they help?
Lymphoma Australia	• Lymphoma Australia offers a wide variety of resources and support for people with lymphoma or CLL and their carers. Please visit our website www.lymphoma.org.au for further information • Lymphoma Australia fact sheets & booklets including: • Booklet: Lymphoma: what you need to know • Emotional impact of a lymphoma diagnosis • Supportive care & living with lymphoma • Lymphoma Australia YouTube Channel: Presentations and interviews on a variety of topics about lymphoma subtypes, management and supportive care. https://bit.ly/2xxdD43 • Lymphoma Nurse Support Line: 1800 953 081 or email: nurse@lymphoma.org.au • Online private Facebook group: ***"Lymphoma Down Under"***: http://bit.ly/33tuwro
International Waldenstrom's Macroglobulinaemia Foundation (IWMF)	• The IWMF support everyone affected by Waldenstrom's macroglobulinemia: www.iwmf.com
WeCan	• WeCan is an Australian supportive care website to help find the information, resources and support services they may need following a diagnosis of cancer. Visit wecan.org.au

SOME QUESTIONS TO ASK YOUR DOCTOR

- Do I need any other tests completed before we decide on what treatment I need?
- What treatment options do I have?
- Is the watch and wait approach appropriate for me?
- Are there any clinical trials available for me even if it means I have to travel further for treatment?

This resource was last reviewed and updated March 2020