



ED FORUM REVIEW: 2010

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INTERNATIONAL WALDENSTROM'S MACROGLOBULINEMIA FOUNDATION

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PRESIDENT'S MESSAGE

BY JUDITH MAY



Judith May, President

This 2010 IWMF Ed Forum Review is devoted to coverage of our 15th annual Educational Forum held in Las Vegas, Nevada. Attendees had the opportunity to hear from renowned researchers and clinicians with expertise in the study and treatment of Waldenstrom's macroglobulinemia.

We are indebted to IWMF Trustee Sue Herms and IWMF members Neal Makens, Michael Greene, and Michael Berndt for providing these comprehensive summaries. We also extend thanks to Alice Riginos, editor of the Torch, and IWMF volunteers Jack Whelan and Mary Brown, who took photos that appear in these pages.

You may order a set of DVDs of these presentations using the enclosed order form. Or, if you prefer, you may purchase them online at our website www.iwmf.com. The cost is \$35 which includes shipping.

AN INTRODUCTION TO BASIC IMMUNOLOGY IN WM

GUY SHERWOOD, M.D.



Guy Sherwood, M.D.

Immunology is the branch of biomedicine that is concerned with the structure and function of the immune system. There are two types of immunity: innate and acquired (also called adaptive).

Innate immunity consists of those characteristics an individual has at birth and that are always present and available at very short notice to protect the individual from infection. Examples include the protective barriers of the skin and mucous membranes, the cough reflex, the acidic pH of the stomach, specialized proteins such as complement in the blood, and certain immune cells such as neutrophils and macrophages.

For this discussion, we are interested primarily in acquired immunity, which is highly specific for a particular foreign substance (an antigen). An individual needs to have an initial contact with the antigen, which in turns triggers a chain of events resulting in the activation of certain white blood cells (lymphocytes) and the production of antibodies. The acquired immune response improves with each exposure to the particular antigen, and the success of vaccination is based on the efficiency of the acquired immune response.

Proliferation and maturation of blood cells take place in the lymphoid organs and tissues. One of the primary lymphoid organs is the bone marrow, which is the site of development of red cells (erythrocytes), white cells (leukocytes), and platelets. All of these blood cells develop

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from a stem cell called the hematopoietic stem cell and mature through a process called hematopoiesis. Red cells are responsible for oxygen transport to the tissues, white blood cells are important in fighting infection, and platelets are important for blood clotting.

There are several types of white blood cells. Neutrophils are short-lived and are the most common white blood cells found in the circulating blood; they multiply very quickly and are largely responsible for the high white blood cell counts seen in acute infections. Eosinophils, basophils, monocytes, and macrophages are other types of white blood cells, although usually present in much smaller numbers. Lymphocytes are the second most common type of white blood cell, and there are two major types: B (bone marrow derived)-lymphocytes and T (thymus-derived)-lymphocytes.

This discussion will focus on B-lymphocytes, which go through several stages as they mature and ultimately develop into plasma cells. During maturation, they are genetically programmed to code on their exteriors a surface receptor molecule specific for a particular antigen. Stimulated by this antigen, the B-lymphocytes multiply and continue to mature. When they become plasma cells, they are no longer able to multiply but secrete large amounts of antibodies of the same specificity for a particular antigen as that of the receptors on their precursor cells' membranes. These antibodies are capable of attaching to and neutralizing antigens. At the same time, a proportion of daughter cells transform back into resting mature B-cells (memory cells) that are capable of being activated for a subsequent and even more rapid response to the same antigen.

The antibodies (also called immunoglobulins) are roughly Y-shaped. Each immunoglobulin molecule consists of two identical light chains and two identical heavy chains linked together. The heavy chains, twice the size of the light chains, form the central portion of the Y configuration, with a light chain on either side. The two types of light chains are kappa and lambda, and, while they have some molecular differences, they function in the same way. Humans have five different classes of heavy chains which differ in both structure and function, and they are IgG, IgA, IgM, IgD, and IgE. The first three are the most important for this presentation. Each immunoglobulin molecule is bi-functional, meaning that one end (the Fab end) is concerned with binding to the antigen and the other end (the Fc end) can bind to the immune cells.

Immunoglobulins are an amazingly diverse group of molecules. When one considers the millions of different antigens in the environment and the capacity for immunoglobulins to provide enough binding sites to recognize these antigens, we can appreciate the complexity of nature and evolutionary mechanisms. It has been suggested that we produce more different forms of immunoglobulins than all the other proteins of the body put together. How is all this diversity possible? The immunoglobulin genes are formed in B-lymphocytes by splicing together widely scattered bits of DNA located on different chromosomes. Imprecise splicing and mutations can increase the variability into billions of possible combinations.

IgG is the major immunoglobulin in normal human blood and can also be found in the spinal fluid and peritoneal fluid. It is the smallest immunoglobulin and the only one that can cross the placenta, thereby conferring immunity from the mother to the developing fetus. The monoclonal antibodies used in treating various diseases, including cancer,



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are IgG-type immunoglobulins, and IgG is the one most typically produced by cells of multiple myeloma, a type of cancer related to WM.

IgA is usually not present in the blood but in secretions of saliva, tears, sweat, breast milk, the urinary tract, the gastrointestinal tract, and the respiratory tract. It frequently occurs in units of two (dimers).

IgM is also referred to as a macroglobulin because it is the largest immunoglobulin. It predominates in the early immune response to most antigens, although it tends to become less abundant subsequently. An elevated IgM level in normal individuals usually indicates a recent infection, recent exposure to antigen, or recent clinical immunization. IgM, often accompanied by IgD, is the most common immunoglobulin expressed on the surfaces of B-lymphocytes, and thus WM cells typically express both IgM and IgD. IgM usually occurs in units of five (pentamers).

As B-lymphocytes mature into plasma cells, the IgM that they make can in fact change to an IgG, IgA, or IgE class. This is called class switching, and its mechanism is irreversible. It is said that WM cells are unable to undergo class switching due to a defect in the gene or genes that control switching; therefore, WM cells are said to be exclusively “pre-switch.” Because class switching is an event that takes place late in the development of the B-lymphocyte, WM is considered to be a mature B-cell lymphoma. Indeed, WM cells are characterized by the presence of cells that are lymphoplasmacytic, that is cells that have characteristics of both B-cells and plasma cells.

What happens to cause WM cells, or any cells, to mutate and not develop normally? Chemicals (such as from smoking), radiation, viruses, and heredity all contribute to the development of cancer by triggering changes in a cell’s genes. Chemicals and radiation damage genes, viruses introduce their own genes into cells, and heredity passes on alterations in genes that make a person more susceptible to cancer. Most cancers arise from several genetic mutations that accumulate in the cells of the body over a person’s lifespan.

When a cell acquires a mutation, it passes that mutation on to its daughter cells during cell growth and division. Because cells with cancer-linked mutations tend to proliferate more than normal cells, these cells grow in number. If one cell finally acquires enough mutations to become full-blown cancer, subsequent cancer cells will be derived from that one single transformed cell, and this means that the tumor is clonal.

Because we are learning more about the genetics of B-cells as well as the various surface markers and proteins found on and in B-cells, newer treatments for B-cell lymphomas, including WM, are focused on treatments targeted to these markers. These include the monoclonal antibodies such as rituximab, ofatumumab, and Campath. More treatments will follow as we continue to explore the complex pathways of B-cell growth and development.

INTRODUCTION TO WM

ROBERT A. KYLE, M.D.

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*Judith May, IWMF President
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It is important to distinguish WM from IgM MGUS (monoclonal gammopathy of undetermined significance), as well as from multiple myeloma, chronic lymphocytic leukemia, and other B-cell lymphomas. It is also necessary to determine if a particular patient’s WM is smoldering (stable and asymptomatic).

There are several criteria used to distinguish WM from MGUS. Generally speaking, MGUS is characterized by a serum monoclonal protein less than 3g/dL; infiltration of the bone marrow with lymphoplasmacytic cells less than 10%; absence of symptomatic anemia, hyperviscosity, or enlargement of the lymph nodes, liver, and spleen; and absence of constitutional symptoms (such as fever, weight loss, fatigue, or night sweats).

Smoldering WM will exhibit a serum monoclonal protein greater than 3g/dL and/or bone marrow infiltration with lymphoplasmacytic cells greater than 10%, but absence of symptomatic anemia, hyperviscosity, or enlargement of the lymph nodes, liver, and spleen and absence of constitutional symptoms.

Dr. Kyle was involved in a long-term study (1960-1994) in Minnesota of 213 IgM MGUS patients that determined the rate of progression of IgM MGUS to WM, as well as to the related diseases mentioned above. MGUS tended to progress more commonly to WM than to these other diseases. Overall the rate of progression of IgM MGUS to WM was approximately 1.5% per year, while the rate of progression of smoldering WM to symptomatic WM was approximately 11% per year. Dr. Kyle emphasized that neither IgM MGUS nor smoldering WM should be treated because they can remain stable for many years.

In 1944, Dr. Jan Waldenström first described two patients with features of what we now know as Waldenström’s macroglobulinemia. These patients were anemic, had a high erythrocyte sedimentation rate (ESR), hyperviscosity (thickening of the blood), and a high molecular weight immunoglobulin detected in their serum.

Approximately five in 1,000,000 people are newly diagnosed with WM every year, making it a rare disease. It is more common in Caucasians than in African-Americans and occurs more frequently in men than in women.



Typical symptoms of WM are weakness, fatigue, oronasal bleeding, blurred vision, recurrent infections, and numbness and tingling of the hands and feet. A physical examination may reveal pallor, enlarged liver and/or spleen, enlarged lymph nodes, and hemorrhaging of the retinal blood vessels. Kidney and bowel functions are usually normal, and rarely there may be lung infiltrates or pleural effusions. Laboratory tests reveal a high total protein and may include a low hemoglobin, low cholesterol, high ESR, usually normal but sometimes low white blood cell count (WBC) and platelet count, and usually normal creatinine, which is an indicator of kidney function. Lytic bone lesions are rare in WM, in contrast to multiple myeloma.

A serum protein electrophoresis (SPEP) detects the presence of a monoclonal immunoglobulin protein, and immunofixation determines that the monoclonal heavy chain protein is IgM and that it has either kappa or lambda-type light chains. Although approximately 80% of WM patients are of the IgM kappa-type, there appears to be no clinical significance attached to this. Small amounts of these light chains, called Bence-Jones proteins, may be found in the urine of WM patients but are not usually of concern. IgG and/or IgA immunoglobulins are usually decreased in WM patients, and approximately 5-10% have cryoglobulins present. IgM can also be measured by nephelometry rather than SPEP, but because these are different test methods that yield somewhat different results, Dr. Kyle emphasized that one should compare results using the same method rather than going back and forth between methods.

A bone marrow aspiration and biopsy are necessary for the definitive diagnosis of WM. The pathologist will see increased lymphocytes and/or plasma cells in the bone marrow, as well as increased mast cells. The typical WM cells have the following markers, determined by flow cytometry: IgM+, CD5-, CD19+, CD20+, CD23-.

Initiation of therapy is indicated by a diagnosis of WM through detection of monoclonal IgM, demonstration of lymphoplasmacytic cells in the bone marrow, and one or more of the following symptoms: weakness, fatigue, fever, night sweats, weight loss, bulky lymph nodes or symptomatic enlargement of the liver and spleen, anemia, low platelets, symptomatic cryoglobulinemia or cold agglutinin disease, amyloidosis, symptomatic peripheral neuropathy, and symptoms of hyperviscosity syndrome (oronasal bleeding, blurred vision, headaches, altered mental state, loss of muscle coordination, and sausageing of the retinal blood vessels).

Because there is such variability in the type and degree of symptoms among patients, correlation of serum viscosity levels with symptoms is poor. Smoldering WM patients should be observed without therapy and followed every 3-12 months by physical examination and hemoglobin and monoclonal IgM measurements. IgM level alone is not an indication for treatment. The WM patient should not be treated unless there is significant anemia or other symptoms present.

WM: UNDERSTANDING YOUR BLOOD TESTS

DELVA DEAUNA-LIMAYO, M.D.
*Head, Multiple Myeloma Section
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Delva Deauna-Limayo, M.D.

Dr. Deauna-Limayo presented a case study of a 65 year old white male who came to his doctor with headaches, fatigue, decreased energy level, weight loss, tingling and numbness of the feet and fingers, nosebleeds, and blurry vision. On physical examination, the doctor found that the patient was pale and had a fever, as well as swollen lymph glands in the neck and underarms, and enlargement of the liver and spleen.

Laboratory testing revealed a normal white blood cell (WBC) count but decreased hemoglobin and decreased platelets. Total protein was high, but albumin was low. A serum protein electrophoresis (SPEP) showed a monoclonal spike of 3g/dL, identified as IgM-kappa. IgG and IgA immunoglobulins were below normal, the serum free light chain assay showed elevated kappa at 81mg/dL, beta2 microglobulin was high at 3mg/dL, and serum viscosity was high at 4cp.

Subsequent bone marrow aspiration and biopsy showed an 80% infiltration of lymphoplasmacytic cells, and the patient was diagnosed with WM.

The clinical manifestations of WM are due to lymphoplasmacytic cell infiltration, the production of IgM, or a combination of the two. These clinical consequences can be detected and monitored in several ways, one of which is the complete blood count (CBC). Plasma, the liquid part of the blood, makes up approximately 55% of total blood volume, with the cellular part comprising the remaining amount. These cells include the red blood cells (RBCs), which carry oxygen; the platelets, which aid blood clotting; and the white blood cells (WBCs), which fight infections. There are several kinds of WBCs – neutrophils, eosinophils, basophils, monocytes, and lymphocytes. When a CBC is performed, the amounts of these different blood cells are measured and compared against normal values.

WBCs, RBCs, and platelets all arise from a precursor stem cell in the bone marrow. The particular white blood cell involved in WM is the B-lymphocyte or B-cell. As the B-cell matures, it normally develops into a plasma cell or a memory B-cell; however, in WM, the B-cell, instead of progressing normally, stops maturing in the late stages of development



and becomes the typical lymphoplasmacytic cell of WM that produces large quantities of IgM antibody. These WM cells possess characteristics of both B-cells and plasma cells, hence their name. They can be found in the bone marrow and in the circulating blood, and if they are numerous in the bone marrow, they can crowd out the normal developing red and white blood cells. This crowding in turn may cause a decrease in the normal number of cells, reflected in the CBC.

When a bone marrow aspiration and biopsy are performed, the WM cells can be identified not only by their appearance but by a process called flow cytometry. This test looks for the presence or absence of certain antigens (called CD antigens) on the surface of cells, and WM cells typically are CD20+, CD19+, CD5-, CD10-, and CD23-.

A chemistry profile is also very helpful in the diagnosis and monitoring of WM. The total protein of a WM patient may be elevated, as in the case study patient above, and the albumin (the most abundant plasma protein) may be low. A serum protein electrophoresis (SPEP) test measures a monoclonal spike (M spike) in the gamma globulin region that is identified by immunofixation as IgM (the heavy chain part of the immunoglobulin), along with a light chain result of either kappa or lambda. It is also possible to have a quantitative test that measures total IgM, IgG, and IgA immunoglobulins by a different method. WM patients typically have higher than normal IgM and lower than normal IgG and IgA.

An eye exam is very important for WM patients, especially if the IgM is high. High IgM can cause an increase in the thickness of the blood (hyperviscosity). If hyperviscosity syndrome is present, the retinal blood vessels will have a sausage-shaped appearance. Hyperviscosity occurs in about 30% of WM patients, with symptoms such as retinal bleeding, headaches, nosebleeds, shortness of breath, and confusion. Viscosity of the serum part of the blood can be measured – normal serum viscosity is about 1.4-1.8cp. As the serum viscosity increases to around 4cp, the risk of hyperviscosity syndrome increases.

Other tests that can be used to monitor WM include beta2 microglobulin and serum free light chain analysis. Beta2 microglobulin is a protein on the surface of cells, and an elevated amount is an indication of increased tumor load. The serum free light chain assay measures the amount of kappa and lambda light chains that are part of the immunoglobulin structure. Their increased presence is another indicator of tumor load.

WHY WM PATIENTS HAVE HIGH IGM

STEPHEN ANSELL, M.D., PH.D.
*Associate Professor of Medicine
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Stephen Ansell, M.D., Ph.D.

Why do WM patients have high IgM levels? In his presentation, Dr. Ansell discussed the source of elevated IgM, the symptoms it causes, and the treatments used to decrease the concentrations when they get too high. He also provided insight into mechanisms that lead to high IgM concentrations.

When the body senses a foreign substance (antigen), it signals B-lymphocytes (B-cells) to begin dividing and differentiating into plasma cells that make antibodies (immunoglobulins). IgM is normally the first immunoglobulin produced. IgM is a large broad-spectrum immunoglobulin that can react quickly with many antigens. IgA and IgG antibodies are much smaller immunoglobulins that are more “skilled” than IgM and better able to defend against more specific threats. The plasma cells generated later on during an infection normally switch from making the more general IgM to making IgA or IgG.

WM cells, however, are not normal cells. The malignancy in WM arises because these B-cells don’t react normally to the body’s signals. First, they don’t die or differentiate like normal cells when the body directs them to and, second, they can’t switch from making IgM to IgA or IgG like normal cells when they differentiate into plasma cells. The body effectively loses control of both the number of WM cells produced and the amount of IgM each cell produces.

WM cells, in fact, not only make just IgM, but they manufacture only one very specific kind of IgM. The term “monoclonal IgM” is used to describe the extra IgM in WM patients because it is all exactly the same kind of IgM generated from clones of the same abnormal cells.

This led to the second point of Dr. Ansell’s presentation, which was to discuss the problems that arise when the IgM level is too high. He categorized IgM-related problems into three groups: the effects on circulation, the interaction with body tissues when deposited, and autoantibody activity.

Circulatory problems can be caused by hyperviscosity. Hyperviscosity occurs when the concentration of IgM, a large antibody, reaches levels that cause the blood to thicken. The resulting poor circulation can lead to many symptoms. Raynaud’s syndrome (whiteness or blueness of the extremities)



may be produced when circulation is inadequate to keep extremities warm in cold weather. Confusion, headache, fatigue, and skin ulcers can occur when oxygen supplies are inadequate for proper functioning of the brain and/or maintenance of various tissues of the body. Blood vessels in the eye can also become expanded (a process referred to as saugaging) and blood can leak out. Gums might also bleed.

Other symptoms are caused by the tendency of IgM to bind to other substances in the body – the severity and types of symptoms will depend on what your IgM reacts with. These can include nerves, skin cells, red blood cells, platelets, and other antibodies. In some cases, the reactivity leads to clumping and deposition. Red blood cells might clump together into stacks referred to as “rouleaux.” When the interaction is with platelets, the result is thrombocytopenia. Interaction with nerve cells causes peripheral neuropathy.

If the IgM-related symptoms are severe, the quickest way to get IgM down is through plasmapheresis. This is only a temporary fix because it removes some of the IgM from the bloodstream but doesn’t stop IgM from being produced. The underlying disease must be treated to produce a long-term IgM decrease. There are a number of reasons to consider plasmapheresis. Generally, if IgM and/or viscosity are high and the patient has one of the symptoms listed previously, he might consider plasmapheresis. Also, it may be a good idea to use plasmapheresis in anticipation of a temporary treatment-related increase in IgM, often referred to as a “flare”.

The final portion of Dr. Ansell’s presentation described the signaling mechanisms in the body that cause elevated IgM. Signals are sent by production of chemical compounds referred to as cytokines. BlyS (B-lymphocyte stimulator) is a cytokine that is critical for maintaining normal B-cells and for immunoglobulin production. Too much BlyS in mice is known to cause lymphoma. BlyS is often over-expressed in WM patients and has been shown to increase IgM production in WM cells. BlyS appears to collaborate with other cytokines to increase IgM.

IL-6 (interleukin 6) is another important cytokine often linked to high IgM. IL-6 is produced during inflammatory events in the body. This cytokine has been shown to cause B-cell proliferation and differentiation as well as stimulate T-cell proliferation. IL-6 levels are often elevated in WM patients, and it has been shown that increasing this cytokine can lead to an increase in IgM production by WM cells.

Recently it has been found that WM patients with very high IgM levels have high levels of another cytokine called CCL5. CCL5 is produced by WM cells and linked to production of IL-6.

Understanding the IgM-related cytokines such as BlyS, IL-6, and CCL5 is important because interfering with one or more of them may provide future treatment options.

Dr. Ansell answered several questions pertaining to IgM production. One questioner asked if anti-IL6 treatment has been tried to reduce IgM production, and Dr. Ansell replied that it has shown biological activity but resulted in only a modest clinical benefit. Another questioner asked which cells make the IgM in WM – B-cells or plasma cells. The answer was that both do – each WM plasma cell makes more than each WM B-cell individually, but there are usually many more B-cells than there are plasma cells.

There was also interest in the usual length of Rituxan-related flare. Dr. Ansell replied that it varies, but commonly IgM increases in the first week or two following treatment and declines in the next month or so.

Another questioner wanted to know if IgM causes the body not to absorb iron. Dr. Ansell said that it is not IgM that causes this, but that it is probably related to IL-6 production. An additional question addressed triggers that cause the disease to kick into high gear. He replied that we don’t always know. Disease progression can occur because of a genetic change or because, for whatever reason, the body begins to send out new signals that cause the disease to progress.

SIGNS, SYMPTOMS & COMPLICATIONS OF WM

MARVIN STONE, M.D.

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Marvin Stone, M.D.

The signs and symptoms of WM can be due to the proliferation of the typical WM lymphoplasmacytic cells, to the level of circulating monoclonal IgM, or to a combination of both factors.

When Dr. Jan Waldenström first described two patients in 1944 with what we now call WM, he noted that both had hyperviscosity (thick blood), their symptoms were distinct from those of multiple myeloma, one of the patients had a cryoglobulin present, and a giant molecule in the serum appeared to be the cause of their hyperviscosity.

The giant molecule was determined to be IgM or immunoglobulin M, which is one of the five classes of immunoglobulins (antibodies) and is the first formed after exposure to antigen. IgM tends to develop pentamers, or structures with five linked molecules, and is very efficient at fixing complement, which is a group of serum proteins that work with antibodies to destroy pathogens. The half-life of



IgM is approximately 10 days, and 80% of it is intravascular (circulating in the bloodstream). Total IgM (normal and monoclonal) can be measured by nephelometry, but the only way to determine if a monoclonal IgM is present is by serum protein electrophoresis (SPEP) and immunofixation – in this way, monoclonal IgM will appear as a spike in the gamma globulin region of the SPEP that can be identified and quantified.

In the peripheral blood smear of a WM patient, one may be able to see the plasmacytoid lymphs, which have characteristics of both lymphocytes and plasma cells, and rouleau formation of the red blood cells. Rouleau is the coin stack-like appearance of the red blood cells that occurs when IgM in the plasma coats the red blood cells and causes them to stick together. In the bone marrow, the pathologist will see the characteristic WM cells, again with features of both lymphocytes and plasma cells. Therefore, WM is a distinct entity characterized by bone marrow infiltration with lymphoplasmacytic lymphoma (low grade) and monoclonal IgM.

WM patients have a median age of 63 years and are more commonly male than female. Signs and symptoms may include weakness and fatigue, bleeding (oronasal), recurrent infections, dyspnea (shortness of breath), congestive heart failure, and varied neurological symptoms. On physical exam, patients may exhibit pallor, purpura (red or purplish skin discolorations), lymphadenopathy (enlarged lymph nodes), hepatosplenomegaly (enlarged liver and spleen), and “sausaging” of the retinal veins (a diagnostic indication of hyperviscosity). The bone marrow is always involved in WM, and there is also frequently proliferation of mast cells in the marrow. Serum IgM concentrations can vary widely, and no IgM value can clearly distinguish between MGUS (monoclonal gammopathy of undetermined significance) and WM. The characteristic WM cells have the following immunophenotype: surface IgM, CD19+, CD20+, CD22+, and CD79+. There are no defining cytogenetic abnormalities, and lytic bone lesions and renal failure are rare.

One of the more frequent complications of WM is hyperviscosity syndrome, which occurs when signs and symptoms develop as a result of high serum viscosity. In addition to retinal vein sausaging, these signs and symptoms include skin and mucosal bleeding, blurred vision, headache, dizziness, vertigo, ataxia (lack of muscle coordination), encephalopathy, or altered consciousness. An IgM level greater than 3g/dL puts one at greater risk for developing hyperviscosity syndrome. Serum viscosity is measured by a viscometer – normal serum viscosity is 1.4-1.8cp, but hyperviscosity is unlikely to occur unless the serum viscosity is greater than 4cp. However, the level of IgM that can cause hyperviscosity syndrome varies between patients. The most rapid (but temporary) treatment for reducing hyperviscosity is plasmapheresis.

Another complication of WM is cryoglobulinemia. Cryoglobulins are immunoglobulins that precipitate or gel at

temperatures less than body temperature (37°C) and reversibly re-dissolve as temperatures again increase. Cryoglobulins are present in 10% of WM patients. Cryoglobulinemia may be caused by a single monoclonal immunoglobulin or a combination of immunoglobulins such as IgM-IgG that form an immune complex (mixed cryoglobulins). Some patients with cryoglobulinemia have no symptoms, but in others symptoms can be significant, as the antibody complexes can affect skin (e.g. blue or white fingers, toes, earlobes, and tip of nose), joints, central nervous system, kidney, liver and spleen. The main prevention for symptomatic cryoglobulinemia is avoiding exposure to cold.

Hepatitis C plays a significant causative role in mixed cryoglobulinemia. About 10% of these patients go on to develop a B-cell lymphoma such as WM. It has been suggested that this type of chronic antigen exposure may cause the development of a malignant monoclonal antibody-producing B-cell population. Treatment of hepatitis C with interferon may also be effective in reducing cryoglobulins as well as reducing the lymphoma tumor burden.

Yet another potential complication of WM is chronic cold agglutinin disease. In this situation, the IgM antibody binds to surface antigens on the patient’s own red blood cells at temperatures less than 37°C. Although cold agglutination occurs at lower temperatures and some of the symptoms may be similar (blue or white extremities) to cryoglobulinemia, it is not the same phenomenon. In severe cases of cold agglutinin disease, hemolysis of the red blood cells can occur, leading to a condition called hemolytic anemia. Treatments include avoiding exposure to cold, plasmapheresis, and rituximab.

One of the most common consequences of WM is peripheral neuropathy, characterized by numbness, tingling, or pain in the extremities. In this case, the IgM is binding to components of the peripheral nerves, such as the myelin sheath, or to the actual nerve cells.

Amyloidosis can be another complication of WM. It occurs when all or part of the monoclonal IgM protein deposits in various tissues and organs of the body, causing damage and dysfunction. Symptoms depend on the type of tissue or organ affected.

It is important to remember that a WM patient will not exhibit all of these possible complications, as the presentation and tempo of the disease vary considerably from patient to patient. It is also important to note that complications may arise not only from the disease itself, but from some of therapies used to treat the disease. These may include low blood counts, immunosuppression/infections, neuropathy, thrombosis (blood clots), and IgM flare.



FIRST LINE TREATMENTS AND HOW TREATMENT WORKS

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There are several indications for therapy in WM patients. These include anemia (hemoglobin <10g/dL), low platelets, hyperviscosity, amyloidosis, symptomatic peripheral neuropathy, symptomatic cryoglobulinemia or cold agglutinin disease, and constitutional symptoms such as weakness, fatigue, fever, night sweats, oronasal bleeding, blurred vision, enlarged liver/spleen, and bulky lymph nodes. Dr. Gertz emphasized that IgM level in and of itself is not an indication for treatment.

There are several broad classes of options available for treatment. These include alkylating agents, purine nucleoside analogs, and monoclonal antibodies. Dr. Gertz compared them and discussed how they work to treat WM.

The most commonly used alkylating agents are chlorambucil (Leukeran), cyclophosphamide (Cytoxan), and melphalan (Alkeran). These generally result in response rates of 70%, with a time to response of 6-12 months. The duration of treatment is 12-24 months. Several of these are oral drugs

that can be taken for longer periods, and their cost is relatively low. The main side effect is moderate bone marrow suppression resulting in a lowering of blood counts. Use of these drugs can be toxic to stem cells and can cause bone marrow damage long-term.

The alkylating agents work by interfering with cell division. When a cell divides, the double strands of DNA have to first separate or “unzip” in order to make a copy so that each copy

can go to a daughter cell. The functional part of the alkylator molecule binds into the unzipping strands of DNA, locks the strands, and prevents them from additional unzipping. Therefore, the cell cannot replicate itself. In this way, alkylating agents prevent WM cells from replication.

The purine nucleoside analogs include cladribine (2CdA), fludarabine, and pentostatin. These treatments have response rates of 70-80%, with a time to response of 1.5-5 months. Duration of treatment is 2-6 months, and their cost is average. They can cause significant bone marrow suppression, opportunistic infections, stem cell toxicity, and long-term bone marrow damage.

Purine nucleoside analogs work on DNA in a way different way from alkylators. The DNA molecule is composed of four nucleobases that form the DNA “alphabet.” The varying combinations of these bases result in the genes that code for proteins. The purine nucleoside analogs are modified molecules which “look” like some of these bases, tricking the

cell into incorporating them instead of the normal molecule. When the analogs are incorporated, the cells, including the WM B-cell, are no longer able to divide.

The monoclonal antibody commonly used in WM treatment is rituximab (Rituxan), which has a partial response rate of 55%, and a time to response of 3-5 months. The duration of treatment is typically 1 month (4 weekly infusions) and its cost is relatively high, but there is no bone marrow suppression and no stem cell toxicity. Other than infusion reactions, the major complication of rituximab use is IgM flare, a temporary increase in IgM.

Rituximab targets the CD20 protein found on the surface of all B-cells, including WM cells. Once it binds to CD20, it attracts the normal immune components (immune cells and complement) of the body to help destroy the B-cell.

Dr. Gertz outlined front-line therapy recommendations of the Consensus Panel from the Fourth International Workshop on WM. These treatments include combination therapy such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or DRC (dexamethasone, Rituxan, cyclophosphamide) and single agent therapy such as Rituxan, purine nucleoside analogs, and alkylators.

Dr. Gertz also presented an algorithm from the Consensus Panel for patients requiring front-line therapy. If a patient is a candidate for future autologous stem cell transplantation and the symptoms that warrant treatment are cytopenias (decreased cell counts), the recommended treatment is DRC or Rituxan/thalidomide. If symptoms from hyperviscosity warrant treatment, the recommendation is Rituxan/CHOP or DRC. For patients who are not candidates for stem cell transplantation and who have cytopenias, the recommended treatment is DRC or Rituxan/thalidomide. Such patients who have hyperviscosity can be treated with purine nucleoside analog/Rituxan or purine nucleoside analog/Rituxan/cyclophosphamide. For non-transplant candidates with comorbidities, who are elderly, or who have slowly progressing disease, Rituxan and/or chlorambucil is the preferred therapy.

Mayo Clinic is attempting additional investigational efforts to improve response rates and the time to relapse by adding lenalidomide (Revlimid) to DRC therapy and by studying the new CD20 antibody called ofatumumab. Other treatments currently being investigated are CyBor-D (cyclophosphamide/bortezomib (Velcade)/dexamethasone) and CyBor-D/Rituxan. Sorafenib and RAD001 are oral investigational drugs that are receiving considerable attention, particularly because of the convenience of oral therapy. Mayo Clinic is included in a major drug study involving Rituxan/bortezomib (Velcade)/dexamethasone and Rituxan/RAD001/dexamethasone.

Dr. Gertz believes autologous stem cell transplant is being under-utilized in younger WM patients. He suggested that these patients consider banking of their stem cells early in the course of their disease before they have received multiple treatments that may harm their bone marrow and make future transplantation impossible.

He also suggested that patients should visit the website www.msmart.org, sponsored by the Mayo Clinic, which outlines treatment recommendations for WM, among other related diseases.



Morie A. Gertz, M.D.



RITUXIMAB MONOTHERAPY FOR WM

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Joseph Mikhael, M.D., M.Ed., FRCPC

Dr. Mikhael began with a brief overview of blood cells. There are three types: red cells, white cells, and platelets. Red cells carry oxygen from the lungs to the tissues and circulate back to the lungs. White cells are part of the immune system – some are big, some are small, some fight on the front lines, and others are supportive. Platelets are designed to start the blood clotting process, and platelet problems can cause a tendency for bleeding.

All blood cells are made in the “factory” called the bone marrow. The bone marrow has many different cells, including plasma cells and lymphocytes. WM is a disease of both plasma cells and B-lymphocytes – hence the term lymphoplasmacytic cells – and treatment for WM is frequently a hybrid of treatments used for both multiple myeloma and lymphoma. Plasma cells are normally 1-2% of the bone marrow. Using a military analogy, plasma cells make up the “Special Forces Unit,” whose job it is to make antibodies (immunoglobulins) that are specifically designed to fight against whatever “enemy” they have been exposed to and retain memory when exposed to the “enemy” again. Antibodies are Y-shaped – one end attaches to the “enemy” and the other end triggers other parts of the immune system to fight. Like “enemies” such as bacteria, cancer cells also have targets that can be identified and destroyed by the immune system.

There are many potential targets on the surface of cancer cells, and the best known is CD20. The concept of monoclonal antibody therapy involves creating an antibody that can attach to a surface marker such as CD20 on a cancer cell and triggering the immune system to fight it. Rituximab was the first such monoclonal antibody, and there are “newer” versions such as ofatumumab that also target CD20, as well as monoclonal antibodies that target CD52 and CD38 surface markers on cancer cells. It is important to note that these surface markers are also found on normal cells; therefore, rituximab and other monoclonal antibodies are not “perfect” therapies but they are more targeted than many of the older types of treatments.

Rituximab as a single agent (monotherapy) is a viable treatment option for WM. Early studies on rituximab monotherapy and WM indicated that it achieved a response rate of about 52% in both untreated and previously treated patients, and that one is less likely to respond to it if IgM is greater than 4g/dL or if albumin is less than 3.5g/dL. Rituximab alone may be desirable to use in the following circumstances:

- When combination therapy may be too harsh, for example in an elderly patient or one who has other health issues
- For slow-growing or less bulky disease when rapid disease control is not necessary
- To improve WM-associated neuropathy
- As possible maintenance therapy to prolong the time to relapse
- As therapy that will not impair stem cells in case autologous stem cell transplant is a possible future option

Rituximab is usually given once weekly for four weeks, although other dosing regimens have been used. Response to it may be immediate or delayed, and there is increasing evidence that it can be used for re-treatment when disease returns. Complications include infusion reactions, temporary IgM “flare,” increased risk of infections, and an impaired response to vaccinations.

ED FORUM 2010: LAS VEGAS



Photos courtesy of Jack Whelan and Mary Brown



WM: SECOND LINE THERAPY

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Rafael Fonseca, M.D.

Dr. Fonseca began by stating that there is no single best answer for patients seeking second-line therapy for their disease. It is important at this stage for patients and their doctors to take the time to discuss various therapies, the goals for their treatment, potential benefits, and possible toxicities.

In the process of selecting second-line treatment, there are several principles that should be considered. These include the following:

1. Disease status – How quickly does the treatment need to work? It may be necessary, for instance, to rapidly bring down one’s protein level, and some treatments work faster and more aggressively than others to accomplish this. A more indolent disease course would require less aggressive treatment.
2. Previous treatment – Did the previous treatment work? What was its toxicity and how did it affect quality of life? What was the duration of benefit? In some cases, it may be possible to re-use the first therapy if it gave a good result.
3. Clinical trials opportunities – Clinical trials, in addition to advancing our knowledge of treating WM, may benefit the patient by offering a treatment he would not be able to receive otherwise.
4. Health status of patient – Does the patient have other health issues that may affect the selection of a particular treatment?

Dr. Fonseca enumerated several of the most common second-line therapies, along with a brief description of each one’s benefits and toxicities. He also reminded everyone that these treatments are frequently used in combination.

Rituximab (Rituxan) is safe and well-tolerated, with most problems being infusion-related. Its long-term safety profile is good. Every medication comes with toxicities, but rituximab is a relatively gentle treatment. It can lower a patient’s immune resistance, leaving him more prone to infections.

The purine nucleosides (fludarabine and cladribine) are usually well-tolerated in the short-term and have good activity. The major concern with their use is immune suppression resulting in opportunistic infections. If one has received this type of treatment, he needs to be monitored very closely for at least a year following treatment for any signs of such infections.

The alkylators, chlorambucil (Leukeran) and cyclophosphamide (Cytoxan), are frequently overlooked as second-line therapies but can be a good option, especially for older patients or those who have co-morbidities such as

diabetes or heart disease. Overall, they are well-tolerated and can be taken in pill form. The main issue with alkylators is the lowering of blood counts. There is a small risk that patients who have received alkylators may eventually develop pre-leukemia (myelodysplasia) or leukemia in the long-term. Alkylators are increasingly being combined with bortezomib (Velcade), and this combination seems to work quite well.

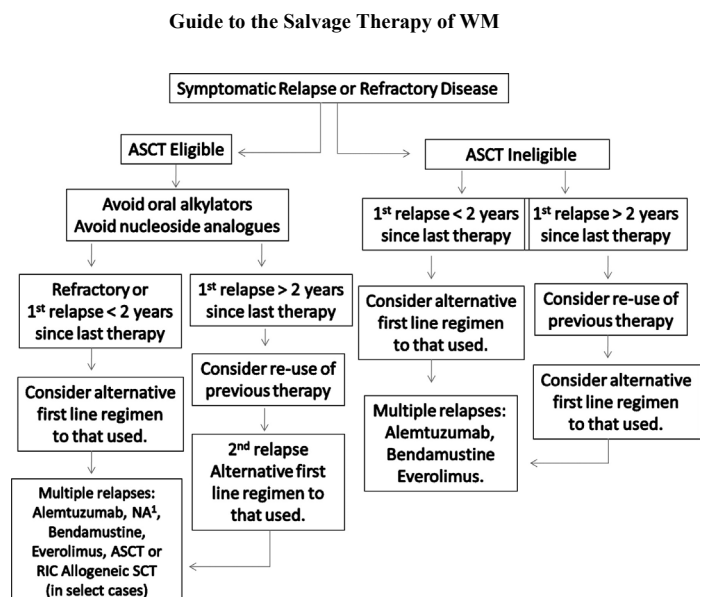
The IMiDs (immunomodulatory drugs) include thalidomide and lenalidomide (Revlimid). They are usually well-tolerated, although lenalidomide carries a risk of anemia, and thalidomide can cause peripheral neuropathy, which is usually sensory, causes numbness but not pain, and is sometimes permanent. Both drugs are taken in pill form and are slower-acting than some of the other therapies.

Bortezomib (Velcade) is a newer drug that is injectable and well-tolerated. Its main side effects are gastrointestinal upsets and peripheral neuropathy. In this case, the neuropathy may be motor as well as sensory and may be painful as well. Other options are being considered to reduce the chances of developing neuropathy, and these include receiving bortezomib injections once a week rather than the more common twice a week protocol. Bortezomib combines well with other agents.

Bendamustine (Treanda) is also an injectable drug that is well-tolerated and combines well with rituximab. This combination compares very favorably to R-CHOP therapy and with less toxicity. Experience with this drug is still relatively limited in the U.S., but its use is increasing.

Other “big gun” and emerging therapies that may be considered for second-line treatment include R-CHOP, R-CVP, Campath, stem cell transplant, and RAD001 (everolimus). Dr. Fonseca commented that Campath can result in severe immunosuppression and is not a drug he uses very often. Stem cell transplant, on the other hand, has become increasingly safer and may be a viable option.

Dr. Fonseca included the following “decision tree” that was excerpted from a paper written by Dr. Steven Treon entitled “How I Treat Waldenstrom’s Macroglobulinemia.” Dr. Fonseca uses this information in his practice when considering second-line therapy for his patients.



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NOVEL THERAPIES IN WM

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An analogy can be made between the signaling pathways of cells and computer circuitry. Cells have their own circuits or molecular pathways, and one can take advantage of these pathways to develop drugs that inhibit the growth and survival of tumor cells. There are two ways that cancer cells can expand their numbers. One is by active proliferation and the other is by prolonging survival through the prevention of apoptosis, a mechanism that leads to cell death. WM may be considered more a lympho-accumulative disease characterized by a failure of cell death rather than a disease of active proliferation.

WM cells have receptors on their surfaces that specifically bind to particular signaling proteins that originate from sources in the surrounding environment such as immune cells and bone marrow stromal cells, and this binding can trigger internal cellular circuitry that leads to the growth and survival of WM cells. Among these external signaling proteins are the following:

- Interleukin-6 (IL-6)
- Insulin-like growth factor 1 (IGF-1)
- Vascular endothelial growth factor (VEGF)
- Tumor necrosis factor alpha (TNF α)
- Transforming growth factor beta (TGF β)
- Basic fibroblast growth factor (bFGF or FGF2)

A few of the internal signaling pathways triggered by the above proteins are described in this presentation. The first is the PI3-kinase/Akt/mTOR pathway that is initiated by the enzyme phosphatidylinositol-3-kinase (PI3K). PI3K stimulates phosphorylation of various proteins that then call in the Akt molecule. Akt ultimately drives the growth and survival of WM cells by activating various downstream signaling proteins (i.e., proteins that occur farther along the path). The Akt inhibitor perifosine has already been tested against WM. Additional drugs that place barriers along this pathway to inhibit the growth of WM cells have been manufactured and will be available for use in clinical trials in the future.

Another important pathway is the nuclear factor kappa B (NF- κ B) pathway, which is a protein complex that can go to the nucleus and there activate various growth factors and support mechanisms that keep the cell alive. Bortezomib (Velcade) is the prototype of the proteasome inhibitor class of drugs that affect this pathway.

The HDAC (histone deacetylase) enzymes constitute another important class of proteins that can be targeted. Our chromosomes are wrapped around histone proteins, which

protect the DNA. For DNA to be transcribed, it has to be unraveled from around the histone. A chemical that affects the activity of enzymes responsible for unraveling the DNA has the potential to be an active cancer drug.

Also deserving of mention are enzastaurin, an inhibitor of the protein kinase C-beta pathway, as well as the role of microRNAs in WM. At the end of this presentation are listed some clinical trials that are or will be underway during the coming year.

The PI3-K/Akt Pathway and Perifosine

If one can block the PI3K pathway in WM-like cells in a cell culture and in patients' cells, their proliferation can also be blocked. Conversely, blocking this pathway does not seem to prevent the growth of normal B-cells, nor the development of normal cells from progenitor bone marrow cells.

Perifosine, an Akt inhibitor, was used in a Phase II clinical trial involving patients with relapsed, refractory WM. The median number of prior therapies was three. Perifosine was given orally for 28 days per cycle for 6 cycles. The most common toxicities were gastrointestinal (nausea, vomiting and diarrhea), as the GI tract seems to be the area most sensitive to PI3K/Akt inhibitors. Other adverse events included anemia, low white cell counts, and arthritis flare. Thirty five percent of patients demonstrated a response to perifosine – 11% had a partial response (i.e., at least 50% reduction in disease burden) and 24% had a minimal response (i.e., less than 50% reduction in disease burden). Another 54% had stable disease. Similar to the findings in previous studies with other treatment regimens, patients in this study who had a β 2-microglobulin level greater than 3.5 mg/dL had a shorter event-free survival than did patients with lower β 2-microglobulin levels.

One of the ways of testing whether or not a drug is hitting its target is gene profiling. Panels testing thousands of genes are used to detect whether particular genes are under-expressed or over-expressed. The perifosine study revealed that the treatment affected certain genes that would otherwise have given growth and survival cues to WM cells through intracellular pathways and via surface receptors. The evaluation of proteins in the bone marrow is a correlate to gene profiling. In the PI3k/Akt pathway, one of these proteins is GSK (glycogen synthase kinase), which is important in the growth and survival of WM cells. At the end of the perifosine study, a decrease in GSK expression was found both by gene expression profiling and by microscopic examination of immunochemically stained bone marrow slides.

The mTOR Complex and RAD001

Downstream from the PI3K/Akt pathway is the mTOR complex, which receives many growth signals, particularly those from the external environment of the cell. The mTOR proteins (mTOR itself plus several associated proteins) normally become phosphorylated (phosphate groups become attached to the protein), at which point they become activated. RAD001 (everolimus) blocks the phosphorylation of mTOR



and inhibits the activation of the complex but does not block the activity of p-PTEN, a phosphatase enzyme that promotes apoptosis. In preclinical studies, when WM cells were layered onto bone marrow stromal cells, the WM cells grew more actively. When RAD001 was added, however, the growth of WM cells was inhibited. In addition, it was found that the intracellular production of proteins characteristic of PI3K/Akt activation was suppressed in the presence of RAD001.

A Phase II trial of RAD001 in relapsed or refractory WM was conducted at Dana-Farber in collaboration with the Mayo Clinic. The median number of prior therapies was three. Mouth sores were a common adverse effect. Some patients had low red and white blood cell counts, and occasional patients also had a pneumonitis (inflammation of the lung) believed to have been of immune origin. Forty percent of patients had a partial response and 30% had a minimal response. The great majority of patients had a substantial decrease in IgM. Occasional patients had a decrease in their IgM levels without a reduction in the amount of bone marrow involvement by tumor. For this reason, bone marrow biopsies are being increasingly used to evaluate residual disease in clinical trials.

The Nuclear Factor Kappa B Pathway and Proteasome Inhibitors

While the NF- κ B pathway was initially the only point at which Velcade was thought to exert its effect, it has become evident that other factors such as the drug's effect on the bone marrow microenvironment are important in both multiple myeloma and WM.

Dr. Ghobrial recently concluded a trial of Velcade + Rituxan in relapsed or refractory WM. Velcade was only given once a week (in a somewhat higher dose than that used in the prior twice weekly trial) in the hope that this would preserve the activity of the drug while minimizing the neuropathy that commonly occurs in WM patients receiving this drug. Velcade was given for 6 cycles, with Rituxan added in cycles 1 and 4. The overall response rate was 83%. Six percent of patients had a complete response (complete absence of disease markers), 48% had a partial response, and 29% had a minimal response. At two-year follow-up, 23% of the patients had relapsed. The incidence of neuropathy was reduced to 10%, in comparison to the 30% incidence that had been the case with twice weekly Velcade. However, there was a greater incidence of Rituxan-induced IgM flare (20%) with once a week Velcade than there had been with twice weekly Velcade (9%). In addition, the complete response rate dropped from 22% in the previous twice weekly study to 6% in this study.

Dr. Ghobrial is now leading a sequential Phase I and Phase II trial of RAD001 + Rituxan + Velcade. This study is just underway at Dana-Farber. First, patients will receive RAD001 + Rituxan. If these patients do well, then they will receive Velcade in addition to the other two drugs. This first phase will establish safe dosing schedules for these drugs.

If Phase I goes well, then the Phase II study will commence. Low risk patients will receive RAD001 + Rituxan. High risk patients will receive all three drugs. Patient risk is being stratified according to the Morel WM prognostic scoring system.

Two new proteasome inhibitors are carfilzomib and NPI-0052. These agents are currently in trials for various malignancies including multiple myeloma. Preclinical studies suggest that proteasome inhibitors may be more effective if two different members of this class are given in combination, such as bortezomib + NPI-0052. This is known as dual-targeting of the proteasome.

HDAC Inhibitors (LBH589)

Inhibiting histone deacetylase enzymes blocks the unraveling of DNA and exposes the DNA for transcription. In the WM-like cell line BCWM.1 (derived from long-term culture of a WM patient's neoplastic bone marrow cells) and in the cells from three WM patients, histone deacetylase was over-expressed. The new drug LBH589 blocks this enzyme. A Phase II trial of LBH589 in WM is now accumulating patients at Dana-Farber, Rocky Mountain Cancer Center in Denver, Colorado, and at Hackensack Medical Center in New Jersey. Twenty patients are currently enrolled at Dana-Farber; the target number for total enrollment in the study is 37 patients. To date at Dana-Farber, very strong responses have been seen in some patients, including substantial IgM reductions. Side effects include fatigue, diarrhea, nausea, and low platelets.

The PKC Pathway Inhibitor Enzastaurin

Enzastaurin is an inhibitor of protein kinase C beta (PKC β), downstream from the Akt/mTOR pathway. A Phase II trial of enzastaurin in WM patients with relapsed or refractory disease was conducted at Dana-Farber under the direction of Dr. Ghobrial. It is an oral drug that is given daily. Thirty seven patients received the drug – the overall response rate was 30%, and many patients had stable disease for an extended period of time. In the future, enzastaurin could be used in combination with another drug such as Rituxan. Because it is well tolerated, it could also be used as a maintenance drug.

MicroRNAs

One of the ways that genes can be regulated is through microRNAs (miRNAs). These are snippets of RNA that are about 21 nucleotides in length. They can bind to various sensitive points on RNA that has been transcribed from DNA, preventing the RNA from being translated into protein. It has been estimated that 5-30% of human genes may be regulated by miRNAs. There has already been considerable study of miRNAs in the cells of chronic lymphocytic leukemia, comparing them to normal B-cells. The test chips available at the present time allow the evaluation of about 800 miRNAs. From among these, Dr. Ghobrial's group has identified several miRNAs that are over-expressed in WM. From a prognostic standpoint, over-expression of these miRNAs correlated with the severity of disease as measured by the Morel scale.



One of the over-expressed miRNAs, miRNA-155, exerts its effect downstream from the PI3K/Akt pathway and is regulated by that pathway. A feedback loop exists between miRNA-155 and the activity of various elements of the PI3K/Akt pathway. *In vitro* studies with the BCWM.1 cell line showed that an anti-miRNA 155 drug decreased the proliferation of these tumor cells but did not affect their survival. In the future it is hoped that anti-miRNA drugs might be used to decrease cell proliferation and when used in combination with other drugs might be able to affect cell survival as well. In a therapeutic setting the level of miRNA-155 would be measured in the peripheral blood, and an anti-miRNA 155 drug would only be given to patients who had high levels of miRNA-155.

Future Direction of Clinical Trials in 2010-2011

Based on the data acquired by the various studies described above, clinical trials that are available now or in the near future include:

- RAD001 + Rituxan
- RAD001 + Rituxan + Velcade
- LBH589
- BEZ235; INK128 (an mTOR inhibitor that is stronger than RAD001)
- RAD001 + LBH589.

(At the Las Vegas forum this paper was presented by Dr. Steven Treon on behalf of Dr. Ghobrial)

NAVIGATING CLINICAL TRIALS

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*Translational Medicine Leader
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Gwen Nichols, M.D.

Dr. Nichols focused her presentation on why and how clinical trials are used and why they are important for patients. She began by offering a disclaimer that, as an employee of a pharmaceutical company, she would not comment on the use of specific approved or off-label agents or mention any particular clinical trials.

In order to discuss clinical trials, it is important to understand the drug development process. When a new agent is designed or discovered in the laboratory, it must first be tested for its ability to kill tumors *in vitro*, i.e. in the test tube. If it shows some promise, it must be further tested to see whether it can be synthesized, purified, and manufactured in a form to be given to patients. If it passes these technical tests, it may be tested for safety on animals. Then an Investigational

New Drug (IND) application is made to the Food and Drug Administration (FDA).

This is followed by years of testing for safety and efficacy and meetings with the FDA to report progress and seek approval for moving forward. Finally a drug will be considered ready for clinical research and submitted to Institutional Review Boards for ethical review.

There are three phases of clinical trials. Phase I trials typically involve about 50 patients to determine the safety of the drug. Phase II trials include 100-200 patients and are concerned with effectiveness and dosage. Phase III trials, involving hundreds of patients, test the new drug against other standard treatments or placebos to determine whether the drug is more effective than alternative treatments. These randomized Phase III clinical trials are particularly difficult to do for WM because so many patients must be recruited and approved. After clinical trials are complete and an application for approval supported by all clinical research data is submitted, it still may require years for the FDA to make a decision for final approval.

In short, drug approval is a long, cumbersome, and expensive process. It can take a dozen years and hundreds of millions of dollars. Many volunteer patients are needed for trials to demonstrate safety and effectiveness. Most new drugs fail to make it to the shelves. Thus, a disease with few patients to participate in trials and few to buy the drugs may be unprofitable for drug companies to research for new treatments.

One way to help alleviate this problem is orphan drug designation, which provides incentives for drug companies to develop treatments for rare diseases. A rare disease (such as WM) is classified as such under the Congressional Orphan Drug Act and is defined as one that affects less than 200,000 people in the U.S. Altogether, there are almost 7,000 such rare diseases, which cumulatively affect 25-30 million people. Orphan drugs amount to less than 15% of all drug approvals by the FDA.

Fortunately there is another path for treatment of rare diseases – off-label use of drugs. These include drugs that have FDA approval, but for a different disease, such as drugs approved for other lymphomas and used to treat WM patients. In the U.S., half of all chemotherapy is for an off-label condition. Off-label use depends on the willingness of insurance companies to pay, which in turn depends in part on the availability of information concerning safety and effectiveness of the treatment on patients for whom it was not originally intended. Further, when drugs are used off-label, patients may have different side effects and different outcomes, and the valid information that could help other patients is often lost because it is unreported.

This gap is filled in the United States in part by the Centers for Medicare and Medicaid Services (CMS). Federal law requires the Medicare program to pay for the off-label use



of a therapy for a specific cancer if it is listed in an approved drug compendium or if at least two articles in peer-reviewed journals support its use. Then insurance companies can be persuaded to pay, and many states have laws requiring that insurers cover off-label use. But both FDA approval and compendium listing for off-label use require clinical trials.

It is critical for WM patients to participate in clinical trials. Some will benefit directly from receiving drugs at no cost. Others will benefit because their insurers require FDA approval or compendium listing, both of which require trials. All need the safety of understanding the differences between WM and other lymphoid malignancies.

How can WM patients get information and gain access to clinical trials? Information is directly accessible from www.cancer.gov; the IWMF website, www.iwmf.com; and one's own physician. On the web, one should search under lymphoma and lymphoid disorders as well as WM.

When a patient contemplates joining a clinical trial, there are several questions that should be asked of one's own doctor and those running the trial.

What is the scientific rationale for use of this agent for WM?

Has it been used on humans before and what are the expected side effects?

Will the cost of treatment for side effects be covered?

How is the treatment given and for how long?

How many follow up appointments, blood tests, biopsies, and other tests will be required?

There is now a new focus on "Personalized Health Care." Agents are being developed for certain classes of patients or to reduce certain specific side effects. Some treatments may be a cocktail of specific inhibitors instead of toxins that hurt all cells. This concept may be helpful for patients of WM and other orphan diseases, but may also make it more difficult to accrue the numbers of patients needed to participate in clinical trials. It will take cooperative efforts by groups like the IWMF to advocate the search for drugs targeted to their disease and to help identify and recruit patients with different defined characteristics in order to speed drug development. Such groups can work with WM researchers who will then approach the pharmaceutical industry with a "proof of concept" for this type of drug development.

Another difficulty with drug development is that companies which sponsor clinical trials only collect data related to the actions of their own drug; therefore, researchers do not have the patient information that would help support the personalized drug concept. The development of an independent patient data base for WM would provide an important tool for advocacy and design of WM clinical trials and the development of effective new therapies.

ALTERNATIVE THERAPIES FOR WM: VACCINES & T-CELL THERAPY

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Immune-based therapy is a relatively new method of treatment for cancer. The immune system includes many types of cells and tissues to protect us from bacteria, viruses, and even cancer. The infection-fighting cells of the innate portion of the immune system (natural killer cells, macrophages, neutrophils,

basophils, eosinophils, etc.) recognize foreign substances but are very general in their response. They also signal the cells of the adaptive portion of the immune system (B-cells and T-cells), which then develop a very specific response to an initial infection and can react very quickly if a person becomes re-infected with the same foreign substance. This property of the adaptive immune system enables vaccination to be a very effective way of preventing certain infections.

This presentation focused on T-cells and T-cell based therapies for cancer. T-cells in particular recognize small fragments of viruses called peptides – each T-cell clone recognizes one very specific peptide. There are approximately 25 million different T-cell clones that recognize viral peptides and can attack and destroy any cell that is infected by a virus. In the same way, T-cells can also work against cancer cells. A study of ovarian cancer found that patients who have many T-cells in their tumor at diagnosis tended to survive longer than those who didn't because these T-cells were fighting their cancer.

What can be done to improve the T-cell immune response in patients who don't have many T-cells in their tumors? How can their T-cells be improved to recognize cancer cells and attack them? Various methods have been tried, some with more success than others. These include injection of T-cell growth factors such as interleukin-2 (IL-2), the development of vaccines, and adoptive T-cell therapy.

T-cell growth factors and vaccines rely on the ability of the patient's own immune cells to mount a response to the cancer cells; therefore, the patient's immune system has to be in reasonably good shape. This may be difficult for patients who have had several treatments with chemotherapies that suppress the immune system.



In vaccine therapy, the T-cells recognize something unique to an individual's tumor that is different from his normal cells – in the case of a B-cell lymphoma this could be the variable portion of the monoclonal immunoglobulin produced by the patient's lymphoma cells. This variable portion is called the tumor idiotype. Idiotype vaccines have been tested in clinical trials for follicular lymphoma, with some positive results but no cures. There is also promise for idiotype vaccine treatment in multiple myeloma, and WM may be a candidate as well.

Adoptive T-cell therapy has an advantage over T-cell growth factors and vaccines because it doesn't depend on the health of a patient's immune system to work. It requires tumor reactive T-cells that can be identified; then these T-cells are removed, greatly expanded in the laboratory setting, and re-infused into the patient with the expectation that the increased number of T-cells will travel through the body and eliminate residual disease. In humans, this therapy has been used in clinical trials for metastatic melanoma and achieved tumor regression in approximately 50% of patients.

New immune therapies for WM could be based on either the idiotype vaccine or adoptive T-cell approach. First, a good target should be identified, and then the T-cells that recognize that target should be identified – the latter is required for adoptive T-cell therapy but also important for a vaccine strategy. Ideally, to get the best response there should be more than one target on the tumor – this might include the idiotype as well as new targets identified through advanced DNA sequencing. Therefore, the next generation of immunotherapy will take a patient's tumor sample, identify all the mutations in that sample, personalize a vaccine targeting all the mutations, and stimulate the specific anti-tumor T-cell response in order to eliminate the tumor cells.

The British Columbia Cancer Agency, with the financial assistance of WM Foundation of Canada, is investigating this type of immune-based therapy for WM. The first target candidate for this therapy is the EZH2 gene, which is mutated in 27% of follicular lymphoma patients and 44% of diffuse large B-cell lymphoma patients. The group is currently testing whether this particular mutation is also a valid target in WM. In addition to assessing this mutation, the group is also looking at other mutations that might be potential targets, as well as identifying tumor-specific T-cells that can be enhanced for better killing of the cancer cells.

WM: ADVANCES IN TREATMENT

STEVEN P. TREON, M.D., M.A., PH.D.

*Director, Bing Center for Waldenstrom's Macroglobulinemia
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Dr. Treon first outlined Consensus Panel Recommendations for the initiation of therapy for WM. These include the following:

- Hemoglobin \leq 10g/dL on the basis of disease
- Platelets \leq 100,000mm³ on the basis of disease
- Symptomatic hyperviscosity ($>$ 4.0cp)
- Symptomatic peripheral neuropathy
- Symptomatic cryoglobulinemia, cold agglutininemia, amyloidosis or symptomatic autoimmune related events on the basis of disease

Dr. Treon then talked about several important topics in therapy currently being used or contemplated for use in WM.



Steven P. Treon, M.D., M.A., Ph.D.

Anemia in WM

Anemia is one of the most common reasons for treatment. Anemia can be due to several factors, among them: crowding of the normal bone marrow cells, high IgM levels which cause a dilution effect in the blood, hemolysis, a side effect of therapy, and iron deficiency because of increased levels of a substance called hepcidin. IL-6, a signaling molecule, drives

hepcidin production, and IL-6 levels tend to be elevated with higher tumor cell involvement. As hepcidin increases, it excites macrophages to gobble up iron and reduces iron absorption in the gut. Therefore, the higher the hepcidin level, the lower the hematocrit. Rather than using a shotgun approach to treat WM if the patient's primary symptom is anemia, one may be able to treat the iron deficiency with intravenous iron rather than oral iron and delay or prevent the use of chemotherapy.

Rituximab

The use of rituximab for WM has increased over time, and today it is considered primary therapy for WM. It is important that physicians realize the significance of the IgM "flare" phenomenon that can be induced by rituximab use. An increase in IgM following rituximab does not necessarily mean that the patient is failing treatment. It does need watching, however, so that the patient does not develop complications from hyperviscosity related to flare.



It has been demonstrated that rituximab in combination with other drugs results in an improvement in response rates. Standard rituximab (x 4 doses) results in 25-30% responses; extended rituximab (x 8 doses) results in 40-45% responses, and rituximab in combination therapy results in 70-90% responses. Complete responses (complete absence of disease markers) are more common in rituximab combination therapy as well. One of the goals of treatment research is to increase the rate of complete responses. The better the response, the longer the progression-free survival; that is, the longer the disease is in check.

Response to rituximab therapy is dependent to a great extent on one's genetics. It has been shown that the FcγRIIIA polymorphism on a patient's immune cells can significantly impact response rates. Patients can now have a test for this genetic polymorphism, which is offered by a company called PGxHealth. Researchers are currently attempting to engineer improved versions of rituximab that will work well for patients who don't have the preferred polymorphism.

Nucleoside Analogs

Long-term follow-up of WM patients has resulted in significant discoveries regarding treatment with nucleoside analogs such as fludarabine and cladribine. NA-treated patients have a 7-fold increased incidence of transformation to aggressive lymphoma and a 3-fold increased risk of developing myelodysplasia or acute myeloid leukemia. The good news is that if transformation to a more aggressive lymphoma occurs, patients can be effectively treated using CHOP-R salvage therapy.

Immunomodulatory Agents

Thalidomide and lenalidomide (Revlimid) are immunomodulatory drugs that excite a patient's immune cells to destroy tumor cells that are exposed to rituximab. Several clinical studies have been performed using both drugs. Unfortunately, thalidomide caused peripheral neuropathy in 44% of WM patients, although this may be ameliorated with dosing adjustments. Patients receiving lenalidomide developed drastic decreases in their hematocrit. These side effects point to the critical importance of involving WM patients in clinical trials and of not assuming that treatment benefits and side effects will necessarily be the same in WM patients as in patients with related diseases.

Pomalidomide is a newer drug in the same class as thalidomide and lenalidomide and appears to be more effective. Because of its promise, Dana-Farber will be testing WM patients in a Phase I clinical study of pomalidomide/dexamethasone/rituximab.

Bortezomib-Based Therapy

Bortezomib (Velcade) has been used in combination with dexamethasone/rituximab and rituximab for WM as front-line and salvage therapy. Response rates have ranged from 80-90% with complete response rates of 5-22%. Peripheral neuropathy has occurred in 10-30% of patients, with a dosing regimen once weekly rather than twice weekly resulting in a lower incidence of neuropathy. Shingles risk increases with bortezomib-based therapy, and prophylaxis with acyclovir or Valtrex is strongly recommended.

A new study which Dr. Treon anticipates will receive approval is a randomized trial of cyclophosphamide/dexamethasone/rituximab (CDR) combination vs. cyclophosphamide/bortezomib/dexamethasone/rituximab (CBDR), followed by maintenance therapy with rituximab alone or with bortezomib/dexamethasone/rituximab. Follow-up will last four years with this study.

RAD001

Both Mayo Clinic and Dana-Farber participated in a study of oral RAD001 (everolimus) in relapsed/refractory WM. The single-agent response rate was 72%, and the main side effects were thrombocytopenia, mucositis, and hyperglycemia. Another trial is being opened for RAD001 as first-line therapy for WM.

Bendamustine

Bendamustine was created in East Germany many years ago and is a hybrid molecule of an alkylating agent and a nucleoside analog. Bendamustine and rituximab combination therapy has been tested against CHOP-R for indolent lymphoma, in a study that included some WM patients. It appears to be more effective than CHOP-R with fewer toxicities – no hair loss, fewer infections, and a lower incidence of neuropathy. Dana-Farber will be starting a Phase II study of bendamustine and rituximab in relapsed/refractory WM, followed by maintenance rituximab for two years.

Additional Comments

Dr. Treon raised some final points regarding treatments. He believes that the impact of maintenance rituximab therapy appears very promising in WM, and he also predicts that autologous stem cell transplant will be more common in WM because patients can benefit from long-term control of their disease. He announced that the Harvard Consortium for Neuropathic Studies in the Lymphoplasmacytic Disorders has been formed to study both disease-related and treatment-related peripheral neuropathy. He also pointed to the significance of the formation of the WM Clinical Trials Group, and suggested that interested persons can go to its website, wmctg.org.



ADVANCES IN THE BIOLOGY OF WM

RESEARCHERS FROM THE BING CENTER FOR WALDENSTROM'S MACROGLOBULINEMIA

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Researchers from the Bing Center: Dr. Steven Treon, Dr. Guang Yang, Thea Ioakimidis, Patricia Sheehy, RN & Zachary Hunter

Decoding Familial WM – Presented by Zachary Hunter

Several years ago, the Bing Center surveyed the medical history of 626 WM patients and discovered that 20% had a first degree relative (parent, sibling, or child) or second degree relative (grandparent, grandchild, uncle, aunt, or first cousin) with WM or a related disorder such as chronic lymphocytic leukemia, multiple myeloma, MGUS, or other non-Hodgkin's lymphoma.

Therefore, a new study was designed to further delineate patterns of familial WM. Those eligible to participate were more than 18 years old and either had WM or a first or second degree relative with WM. Blood samples, clinical data, and genetic information were obtained from the participants, who numbered 492, representing 159 families, at the time of this report.

The study found that the participants fell into three family types, designated as follows:

- WM History – had a first or second degree relative with WM or IgM MGUS – 22 families total
- Mixed B-Cell History – had a first or second degree relative with a B-cell malignancy (not WM) – 57 families total
- Sporadic WM – no history of WM or other B-cell malignancy – 80 families total

The study also found that these family types had some differences in clinical presentations that may represent a difference in the genetic basis of their WM. For instance, hypogammaglobulinemia (low IgG and IgA) is a common finding in WM patients, even if their disease status has improved with treatment. The Sporadic WM families had

significantly lower IgG and IgA levels than the other family types, and the WM History families had more previously undiagnosed MGUS than the other families.

The researchers also looked at two genetic differences that seem to be more common in Mixed B-Cell History families. The two genes are GSTM1 (Glutathione S-Transferase Mu 1) and GSTT1 (Glutathione S-Transferase Theta 1). Both help prevent cellular and genetic damage – the absence of these two genes is associated with increased risk for leukemia, prostate, breast, colon, and lung cancer. Both genes appear to be missing in a larger proportion of the Mixed B-Cell History families; therefore, there may be an association of WM with the absence of these genes.

The Bing Center is in the process of verifying differences in WM patients based on bone marrow cell type, history, and clinical background to better understand the genes and signaling pathways driving WM and to apply this to the various WM family subtypes. It is hoped that better delineation of these patterns will lead to new treatments for WM.

Advances in CD20-Directed Antibody Therapy in WM – Presented by Dr. Guang Yang

Monoclonal antibody therapy has changed the landscape of treatment over the past decade because these drugs have provided significant efficacy but with much less toxicity due to the nature of their specific targeting. To date, the FDA has approved 26 monoclonal antibodies (MABs) for various diseases, and another 200 are in clinical trials – ten MABs have been approved for cancer and of these ten, four are targeted to the CD20 antigen.

WM cells highly express CD20 on their surface. CD20 MABs attack cancer cells in three general ways:

- They bind to CD20 and recruit the body's immune cells by attaching to the Fc receptor on these cells; this leads the immune cells to attack WM tumor cells. This mechanism is called ADCC (antibody dependent cell-mediated cytotoxicity).
- They bind to CD20 and to a protein called complement, which is then activated, leading to a series of enzymatic reactions that result in an attack on the tumor cell membrane. This is known as CDC (complement dependent cytotoxicity).
- They bind to CD20 and directly induce programmed cell death (apoptosis).

Rituximab was the first therapeutic MAB approved by the FDA for cancer. It is a chimeric (part mouse/part human) antibody. The very first antibodies were totally mouse but could not be repeatedly used because of the recipients' reactions to the foreign mouse protein. The chimeric antibodies replaced part of the mouse protein with human antibody. Further refinements have led to humanized antibodies which have a very small mouse portion, and fully human antibodies are now being produced by transgenic mice that have been specifically bred to produce human antibodies.



When the Bing Center began using rituximab in its WM patients, an important discovery was made. That was the significance of the FcγRIIIA genetic polymorphism found on a patient's immune cells – the polymorphism affects the ability of rituximab to bind to the immune cells. At position 158 of this gene, patients will have the amino acid combination of valine/valine (V/V), valine/phenylalanine (V/F), or phenylalanine/phenylalanine (F/F). It was found that patients with at least one valine (V/V or V/F patients) achieved a four-fold higher response rate to rituximab than patients who were F/F. This applied to combination therapy with rituximab as well as with single-agent rituximab.

Improvements in CD20 therapy have resulted in a humanized antibody called ofatumumab (Arzerra) which was approved in 2009 for chronic lymphocytic leukemia patients. It targets a different site (epitope) on CD20 than rituximab and may be better able to destroy rituximab-resistant cells by increasing complement dependent cytotoxicity.

For those patients who have the F/F polymorphism and may not benefit from rituximab, a new CD20 MAB has been developed called GA101. It has been engineered to enhance both antibody dependent cell-mediated cytotoxicity and direct apoptosis, and when compared to rituximab and ofatumumab in the laboratory, it is the most powerful in terms of both of these methods of tumor killing.

Dr. Yang also discussed the mechanism for IgM flare, which is an abrupt increase in IgM frequently seen after the use of rituximab. This temporary flare can be serious if it results in hyperviscosity, and it has been observed with single-agent rituximab as well as rituximab in combination with other drugs. The same IgM flare has also occurred in patients who receive intravenous gamma globulin (IVIg).

What causes flare? The Bing Center carried out a series of experiments to find the answer. Researchers cultured WM cells with rituximab or IVIg but saw very little flare. By adding monocytes (a type of white blood cell) to these cultures, they saw dramatic increases in flare. They theorized that a cytokine (cell signaling protein) might be responsible and found that a cytokine called IL-6 was significantly increased in WM patient monocytes stimulated by rituximab or IVIg use. When IL-6 was removed from the cell cultures, the flare was reduced. They also detected increased serum IL-6 levels in WM patients who flared. These studies may have implications in the development of therapeutics aimed at blocking IgM flare in patients undergoing rituximab or IVIg therapy.

Maintenance Rituximab Is Associated with Improved Progression Free and Overall Survival in WM – Presented by Thea Ioakimidis

Single agent rituximab for WM typically results in an overall response rate (ORR) of 20-30% and progression free survival (PFS) of one year with the standard induction regimen – once weekly infusions for four weeks. Ms. Ioakimidis defined progression free survival as the length of time during and

after treatment in which a patient is living with a disease that does not get worse or receive another treatment. The use of extended rituximab, which is the induction regimen plus four additional infusions beginning at week 12, results in an ORR of 40-50% and PFS of 16-30 months.

Rituximab therapy has been aggressively pursued because it does not suppress the bone marrow and because of its potential to synergize with other agents. Varying combination therapies with rituximab have seen ORR of 70-90% and PFS of 3-4 years. However, despite this success, most WM patients still progress. Therefore, maintenance rituximab has been increasingly studied and used for its potential benefit.

The Bing Center designed a study to identify WM patients who were previously untreated with rituximab but who then underwent rituximab-containing induction therapy, either single-agent rituximab or combination therapy. Patients who achieved at least a 25% decrease in their IgM following induction therapy were split into two arms – one arm was observed and the other arm received rituximab maintenance. This study resulted in a total of 248 patients, 162 of whom were observed and 86 of whom received maintenance.

Progression free survival in the observation arm was 28.6 months vs. the maintenance arm at 56.3 months. Overall survival in the observation arm was 116 months vs. the maintenance arm at greater than 120 months (and still ongoing). The possible or probable adverse events in both groups included arthralgia, bronchitis, encephalitis, pneumonia, headaches, shingles, hypersensitivity, neutropenia, sinusitis, skin infections, fainting, and upper respiratory infections. The only significant difference between the two groups in this regard was the rate of infectious events, which occurred in 20% of the observation arm and 38% of the maintenance arm. Most of these involved the respiratory tract and nearly all were grade 2 or less.

This study also attempted to determine which infusion schedule is best – either four weekly infusions every six months or one infusion every three months. There was no statistical difference in results between the dosing regimens.

Immunoglobulin levels were measured and it was found that IgM levels dramatically decreased in the maintenance group. IgG levels decreased in both groups, slightly more so in the maintenance group, while IgA levels remained about the same in both groups. The maintenance group also had a better hematocrit response, while there was no significant difference in platelet and neutrophil counts between the two arms.

During the follow-up period, a categorical upgrade in the type of response, for example, an improvement from a partial response to a very good partial response, occurred in 10% of patients on observation and in 41.8% on maintenance.

Overall, the study concluded that maintenance rituximab was associated with improved categorical responses as well as prolonged progression free survival and prolonged overall survival.



Peripheral Neuropathy in WM – Presented by Patricia Sheehy, Nurse Practitioner

Peripheral neuropathy (PN) is very important in WM – in some studies up to 47% of WM patients experienced it. It is chronic and progressive, it is symmetric (for example, both feet), it is predominantly distal (starts in the toes and feet because they are farthest from the brain), involves the sensory nerves (numbness, tingling, heat/cold, pain, gait disturbance), and less commonly involves the motor nerves.

There may be contributing factors in PN that are not WM-related and may need to be ruled out as the cause of PN. These include diabetes, peripheral vascular disease, nutritional deficiencies, or overuse injuries. WM-related PN may be due to the following:

- Non-specific direct deposition of IgM on the nerves
- Amyloid – a complex fibrous protein deposited in the tissues
- Specific targeting of nerve components by IgM, including
 - Antibodies to the myelin sheath coating the nerves – called anti-MAG
 - Antibodies to ganglioside, a molecule on the surface membrane of nerve cells
 - Antibodies to sulfatide, a lipid found primarily in the central nervous system

Approximately 30% of IgM-related PN is due to anti-MAG antibodies. Although PN doesn't cause death, it can cause significant disability. PN can be treated but one needs to know the specific reason why it is occurring so that the most appropriate treatment can be selected. Among these treatments are the following:

- Plasmapheresis – removes IgM but is not a permanent solution
- IVIg – may cause IgM flare which can temporarily worsen symptoms
- Rituximab or combination rituximab/chemotherapy – may cause IgM flare which can temporarily worsen symptoms
- Symptomatic control to reduce pain – drugs such as gabapentin (Neurontin), pregabalin (Lyrica), duloxetine (Cymbalta)

The Bing Center performed a retrospective study, looking back at the charts of 900 WM patients, and found that 199 (22%) of these patients had disease-related PN. Of these, only 122 had been tested for neuropathic antibodies such as anti-MAG, but approximately 25% of these were anti-MAG with much smaller percentages of the other specific antibodies. Only 61 patients had been tested for amyloid, and of these, 21% tested positive. Ms. Sheehy said that the Bing Center will be doing more testing for amyloid in PN patients because it appears to be more significant than originally thought. Of those who were treated, 69% had improvement of their PN with plasmapheresis, 12.5% had improvement with IVIg,

and 47% had improvement with chemotherapy. It was also interesting that 5.3% of patients treated with chemotherapy had complete resolution of their PN.

Other results noted from this study included the observation that amyloid patients tended not to have as much improvement of their PN as non-amyloid patients. Patients who had a major disease response from chemotherapy also had a very good PN response, and combination therapy worked better than monotherapy at improving PN. Patients who had PN less than two years had a better response than those who had PN for more than two years – but even so, 40% of patients who had PN for a longer time still had an improvement in their PN.

The study also left the Bing Center with additional questions to answer, and for that reason they have begun to include neurophysicists and neurologists from various institutions in their ongoing studies of PN. Some of these questions include:

- What is the goal of therapy for an individual patient – to prevent worsening or to try for symptomatic improvement?
- Will the timing of therapy make a difference in PN? Should it be treated at an earlier stage?
- What is the optimal therapy for PN?
- Should amyloid patients be looked at differently?
- What is the role of novel agents for WM treatment in PN?
- What is the role of maintenance therapy in PN?
- What type of response criteria should be used for PN – anti-MAG titers, IgM levels, nerve conduction studies?

Moving forward, there will be more targeted clinical trials performed for both WM and multiple myeloma patients with PN. Newer drugs such as pomalidomide, carfilzomib, bendamustine, and newer CD20 antibodies such as GA101 and ofatumumab will be examined, as well as newer drugs for symptomatic relief such as Ampyra, which was just FDA-approved for multiple sclerosis and may be of benefit for WM patients who have PN.





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SAVE THE DATE!

The next IWMF Educational Forum is scheduled
to be held June 24-26, 2011, at the Radisson Plaza Hotel
in Minneapolis, Minnesota. Program details and
registration information will be available shortly.