ED FORUM REVIEW: 2013

PRESIDENT’S MESSAGE

Carl Harrington, President

I am very pleased to present to you this year’s Ed Forum Review, which summarizes most of the presentations from our 18th annual Educational Forum held in San Diego, CA, this past May. Attendees had the opportunity to hear from renowned researchers and clinicians with expertise in the study and treatment of Waldenstrom’s macroglobulinemia. I think you will find the information very important to your understanding of our disease.

We are indebted to our volunteer editorial staff, whose names are listed in the editorial box on page 2, for generously giving their time and effort in writing and editing this special issue. Thanks also go to photographer Jack Whelan and to Sara McKinnie in the IWMF office.

Next year’s Ed Forum will be May 16-18 in Tampa, FL, at the Renaissance Tampa International Plaza Hotel. More details will be forthcoming later this year. Stay tuned and save the date!

UNDERSTANDING YOUR BLOOD TESTS

Robert A. Kyle, M.D.

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Dr. Kyle first discussed monoclonal gammopathy of undetermined significance (MGUS) because all WM patients begin with IgM MGUS. He also compared MGUS to smoldering WM and to symptomatic WM.

Patients with IgM MGUS have a serum IgM less than 3 g/dL in size and a bone marrow infiltration of fewer than 10% lymphoplasmacytic cells, which are the characteristic cells of WM. MGUS patients also have no symptomatic anemia, no hyperviscosity (increased blood thickness), and no enlargement of the liver, spleen, or lymph nodes. There are also no constitutional symptoms present, such as fever, night sweats, weight loss, or fatigue.

In smoldering WM, the serum IgM is equal to or greater than 3 g/dL and/or a bone marrow infiltration equal to or greater than 10% lymphoplasmacytic cells. As in MGUS, smoldering WM patients have none of the symptoms listed above.

Patients with MGUS have a risk of progression of approximately 1.5% per year, while smoldering WM patients have a much higher risk of progression – 12% per year in the first
measures several parameters including hemoglobin, hematocrit, red blood cell count, white blood cell count (with a differential, which is a breakdown of the various different kinds of white blood cells), and platelet count. The hemoglobin, hematocrit, and red blood cell counts are ways of determining the oxygen-carrying capacity of your blood. In WM, these parameters may be lower than normal, causing anemia, which is a frequent symptom of the disease. Hemoglobin is the specific carrier molecule of oxygen to the tissues; normal hemoglobin in males is 13.5-17.5 g/dL and in females 12-15.5 g/dL. The white blood cell count is composed of various cells involved in the immune system, including neutrophils, lymphocytes, monocytes, eosinophils, and basophils. In WM patients, the WBC count is usually normal, unless affected by treatment, although the lymphocyte count may be increased. Neutrophils normally comprise more than 50% of the total white blood cell count, while lymphocytes are normally less than 25% of the total. Platelets assist in blood clotting, and a normal platelet count is around 150,000-450,000 µL; in WM the platelet count is usually normal, although it may be lower in some patients.

Serum protein electrophoresis (SPEP) – separates the proteins in the serum based upon their size and electrical charge. A serum sample is placed on an agar gel and an electrical current is introduced, causing the proteins to migrate on the gel. The proteins can then be stained for visualization, and a densitometer can quantitate the various proteins present, including immunoglobulins, based on their staining density.

Immunofixation – is usually performed along with SPEP and determines whether the particular immunoglobulin in question is IgM, IgG, IgA, etc., and whether the light chains are kappa or lambda type. In the case of WM, the abnormal amount of immunoglobulin present is always of the IgM class.

Quantitative immunoglobulins – a different method for measuring the amount of IgM (or IgG and IgA). This method does not always directly correlate with the value obtained by SPEP. Although the WM consensus panel recommends measuring the IgM by SPEP, Dr. Kyle prefers to order both SPEP and quantitative immunoglobulins. Dr. Kyle emphasized that, if a patient initially has his or her
IgM measured by one method, the same method should be used for all subsequent IgM testing in order to have an accurate way to compare results from test to test. Also, there can be some variation in test results, and he cautioned patients not to focus on one test result but to look for trends in IgM over time. IgG and IgA are frequently decreased in WM, but Dr. Kyle stated that one should not receive intravenous immunoglobulins just because these numbers are low.

**Serum viscosity (SV)** – measures the thickness of the serum in comparison to the thickness of water, which is the standard or control and is 1.8 cp. In WM, the concentration of IgM in the blood may cause a high level of viscosity, known as hyperviscosity. Symptoms of hyperviscosity do not usually appear until the IgM is greater than 3 g/dL and the serum viscosity is greater than 4 cp. The best way to determine if hyperviscosity syndrome is present is for an ophthalmologist to examine the back of the eye in a dilated eye examination and look for “sausaging” and/or hemorrhaging of the retinal vessels.

**24-hour urine collection** – usually performed at the time of diagnosis and involves both electrophoresis and immunofixation. WM patients may have small amounts of light chain proteins, called Bence Jones proteins, in their urine. In rare cases Bence Jones proteins may cause kidney problems.

**Cryoglobulin test** – looks for precipitation of IgM at refrigerator temperature. A small percentage of WM patients have a monoclonal IgM with this characteristic known as cryoglobulinemia. This condition is usually not a problem unless the IgM precipitates close to room temperature, in which case patients can exhibit symptoms of bruising and even tissue necrosis because the precipitated IgM interferes with blood flow, particularly in the extremities.

**Bone marrow aspiration and biopsy (BMB)** – WM patients have increased lymphocytes, plasma cells, and mast cells in their bone marrow. The liquid aspiration will frequently have a low number of cells (a condition designated hypocellular) because the marrow is so packed that it is difficult to draw liquid into the syringe. The actual punch biopsy of the marrow may be packed with the typical lymphoplasmacytic cells of WM (a condition designated hypercellular). The lymphoplasmacytic cells can be diagnosed in the bone marrow because of their appearance, the presence of certain surface markers, and detection with special stains. WM cells have the following surface marker characteristics: IgM+, CD5-, CD19+, CD20+, and CD23-.

**Beta-2 microglobulin and albumin levels** – both can be important in disease prognosis. A normal beta-2 microglobulin level is 0.7-1.8 mcg/mL, and a normal albumin level is 3.5-5 g/dL; in WM patients the level of beta-2 microglobulin is usually increased, while the level of albumin may be decreased.

Dr. Stone opened his presentation with a discussion of the career and discoveries of Dr. Jan Waldenström, beginning in 1944 with two patients. In that sense, WM is a young disease without a long history of experience. Today it is characterized by a monoclonal spike in serum IgM. IgM is one of 5 classes of immunoglobulin, or antibody, a normal part of the immune system. IgM is the largest antibody by far, and some of its characteristics include the following:

- **Structure**: Composed of two heavy chains of µ type + two light chains of either κ (kappa) or λ (lambda) type
- **Molecular weight subunit** 185,000 daltons
- **Present in star-shaped pentamers** (five attached subunits)
- **10 antigen binding sites**
- **Normal serum concentration of 1.5 mg/mL**
- **Half life in serum - 10 days**
- **Fixes complement**, a system of proteins involved in protection against infection
- **80% of IgM is intravascular** (in the circulating blood)
- **First antibody formed after infection**

In WM, monoclonal IgM, also called the M spike, is detected in the serum by protein electrophoresis. The spike occurs because of the presence of a large number of identical (monoclonal) molecules of IgM produced by the tumor cells. Under the microscope, the IgM coats the red cells and makes them sticky. WM cells are intermediate in appearance between plasma cells and lymphocytes, and for that reason the disease is called lymphoplasmacytic lymphoma.

In recent years, it has been recognized that an incidence of monoclonal gammopathy of undetermined significance (MGUS), a precursor of WM and other plasmacytic lymphomas, is found in 15-20% of patients’ families. Most recently, Dr. Steven Treon’s group at Dana-Farber Cancer Institute discovered that a mutation of the MYD88 gene on
chromosome 3 is present in 90% of WM patients and is not present in normal B-cells or in patients with similar diseases. This mutation appears to confer enhanced survival properties in the tumor cells and is the target of research for novel treatments.

WM patients have a median age of 63 years at diagnosis; the disease is more common in men than in women, and WM is less common than myeloma. Symptoms include weakness and fatigue, nosebleeds, recurrent infections, dyspnea (shortness of breath), congestive heart failure, and varied neurological symptoms. Patients can present with pallor, bruising, enlargement of lymph nodes, liver, and or spleen, and “sausaging” of retinal veins diagnostic of hyperviscosity syndrome (HVS).

One of the characteristics of WM is that the bone marrow is almost always involved. There are several varieties of lymphoid cells, plasma cells, Dutcher bodies rich in carbohydrates from the IgM, and an increased number of mast cells. About a third of the patients have enlarged lymph nodes and/or enlarged livers or spleens. But the bone pain and kidney disease often found in myeloma patients are fortunately not present in WM.

Hyperviscosity syndrome may be present, either at onset of WM or as the disease progresses. Symptoms include skin and mucosal bleeding, blurred vision, headache, dizziness, vertigo, ataxia (loss of balance), encephalopathy (abnormal brain function), or altered consciousness. It is associated with a high levels of IgM, usually above 3000 mg/dL, and a serum viscosity above 4.0 cp. Patients have varied tolerance to hyperviscosity because the IgM molecules associated with the disease are different.

The diagnosis of hyperviscosity can be made with a physical examination. Observing the optic nerve at the back of the eye, a physician will see engorgement of the optic blood vessels, giving the appearance of a string of sausages. This is the best indicator of HVS.

Plasmapheresis for the treatment of hyperviscosity syndrome has been used since the 1950s. It is effective because most of the IgM is present in the circulating blood and thus easily removed by this method. Plasmapheresis reverses retinopathy and other clinical manifestations of HVS. Keeping serum viscosity below each patient’s symptomatic threshold effectively prevents recurring HVS. Plasmapheresis is sometimes necessary as an emergency procedure and is useful as maintenance therapy in selected patients who cannot tolerate chemotherapy.

Cryoglobulins are present in the plasma in a percentage of WM patients. They are immunoglobulins (antibodies) that precipitate or gel at temperatures less than 37°C (body temperature) and re-dissolve at 37°C. The phase change is temperature-dependent and reversible. 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.

Another symptom of WM is chronic cold agglutinin disease. Cold agglutinins are anti-erythrocyte (red cell) antibodies (usually IgM) that preferentially bind to antigens on the surface of the red blood cells at temperatures less than 37°C. They account for 30% of immune-type hemolytic anemia, acrocyanosis (bluish discoloration of the hands and feet), Raynaud’s phenomenon (white discoloration of the fingers and toes), and hemolysis (destruction of red blood cells) after cold exposure. Hemagglutination (clumping of the red blood cells) may be grossly visible in blood samples with cold agglutinins. Treatment includes rituximab and fludarabine, usually for three months, with a 70% response rate. There are some complete remissions of more than five years duration.

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.

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**HOW CHEMOTHERAPY WORKS** *(WE THINK!)*

**JOSEPH MIKHAEL, M.D., F.A.C.P.**

*Mayo Clinic, Scottsdale, AZ*

Dr. Mikhael began his presentation by commenting how much better informed patients are than in the past about their disease and treatment options. More knowledgeable patients foster a higher level of communication which should lead to better treatment decisions and outcomes. However, he also reminded the audience that even though the medical community has improved its own understanding of the disease and how different treatments work, physicians still don’t know everything.
Dr. Mikhail half-jokingly compared the components of blood to the three types of wine: white, representing the cells of the immune system; red, the corpuscles that serve as the oxygen delivery system; and rosé for the platelets, which arrive first following an injury and tell the body to bring everything needed to make a clot. All of these blood components are generated in the bone marrow.

Of primary importance in WM are the white blood cells called B-lymphocytes (B-cells) and the plasma cells. These cells are a small proportion of healthy bone marrow and serve the function of producing antibodies (or immunoglobulins). Some B-cells move out and mature in the lymph system and some return to the marrow. WM involves both lymphocytes and plasma cells and it is for this reason referred to as a lymphoplasmacytic cancer. Because it is a disease with both lymphatic and marrow components, it has been treated historically by involving a mix of therapies designed for lymphoma (cancer of the lymph system) and myeloma (cancer of plasma cells in the bone marrow).

The primary treatments fall into four categories: (1) alkylating agents, (2) nucleoside analogues, (3) monoclonal antibodies, and (4) proteasome inhibitors. These are considered “the four pillars” of treatment, each involving a different strategy for attacking cancer cells.

**Alkylating agents** were discovered following WWI when it was realized that soldiers exposed to mustard gas were missing cells in their bone marrow and had diminished spleens and lymph nodes. Chlorambucil, melphalan, and cyclophosphamide are the alkylating agents most commonly used to treat WM. For a tumor (or any group of cells) to live on, the cells must divide to yield new cells. Dividing or unzipping the DNA first is critical to this process. Alkylating agents prevent the DNA from dividing and, thus, cells treated with alkylating agents cannot divide and grow.

Alkylating agents have about a 70% response rate against cancerous cells. However, in addition to cancer cells, they affect healthy cells. This is especially true of other cells in the body that divide rapidly. For example, cells in the GI tract can be susceptible to attack, leading to nausea and diarrhea. Alkylating agents also attack cells in the scalp, which can lead to hair loss. Cells in the mouth lining can be affected by this class of drugs, leading to mouth ulcers. Good blood cells can also be attacked, which can then lead to bleeding (loss of platelets), infection (loss of white cells), and fatigue and weakness (loss of red cells).

**Nucleoside analogs** also affect cell division – not by preventing the unzipping of DNA but by “matching” up the open DNA strands with “dummy” partner molecules. These dummy partners deactivate DNA duplication, rendering further cell growth and division impossible. Fludarabine, cladribine, and clofarabine are some of the drugs in this class. Low blood counts are common following treatment, and there can be serious toxicity to stem cells – making it hard to collect and store stem cells for a possible stem cell transplant later. The reduction in stem cells can also leave some patients with long-term low blood counts and susceptibility to severe infections. Because of this, these drugs are used less frequently than they were in the past to treat WM.

**Monoclonal antibodies** are considered one of the great successes of cancer care in the last 20 years. The concept behind this type of treatment is to marshal one’s own immune system against the tumor. If one’s own immune system is killing the cells, it tends to be easier to tolerate than traditional chemotherapy methods and focuses more specifically on the elimination of the cancer cells with less damage to healthy cells.

The central reactive ingredient in this drug class is the antibody. Recall that many types of antibodies are created by plasma cells in normal marrow to defend against infection. Their structure and composition can be shaped or designed in many different ways, such that they can become very specific to a type of infectious agent, for instance a bacteria or virus. In the case of monoclonal antibodies, one side of the antibody is designed to “hook” to the cancer cell while the other end sends a message to immune system to attack it.

Rituximab was the first in the class of monoclonal (mono = one, therefore specific to target) antibodies, and it was designed to target the CD20 marker on B-cells. CD stands for protein “clusters of differentiation” and assigning a number for each cluster type provides researchers with a quick way to classify them. Nearly all WM cells are initially CD20 positive. Thus, this drug is, in effect, a “smart bomb” designed to affect only the CD20 positive cells and spare the rest. This drug revolutionized lymphoma treatments and has been combined and incorporated into nearly all treatment regimens. However, it can affect other CD20 cells in the immune system and lead to increased infections. There is also a rare brain complication with rituximab use [called progressive multifocal leukoencephalopathy, which occurs as a result of viral reactivation]. A primary observation associated with WM is the IgM flare, which is a temporary increase in the amount of IgM present in the blood following treatment. This effect, when it occurs, can usually be treated successfully.

**Proteasome inhibitors** are one of the newest drug classes in cancer therapy. The concept, based on Nobel Prize winning work in 2004, made it quickly into the clinic by 2005! Bortezomib (Velcade) is the most important drug in this class for WM; however, carfilzomib is another in the same class currently in use. Bortezomib was initially felt to be of use only in myeloma, but it has proven efficacy in many lymphomas, including WM.

All cells have proteasomes that control the way that cells operate. Normal cells are programmed to live for a while and then die. Proteasomes are an important part of this programming circuit. In cancer cells, proteasomes behave in unusual ways that cause cells to divide or die on their own schedule, rather than on a schedule more typical of normal
cells. Proteasome inhibitors are designed to prevent the unusual behavior of proteasomes in cancer cells.

Dr. Mikhael highlighted four other novel agents that are in use. These include mTOR inhibitors (everolimus and others), AKT inhibitors, oral proteasome inhibitors, and novel monoclonal antibodies. Tremendous progress has been made in the field of chemotherapy. New classes of drugs have improved response rates and improved overall survival. Combining “old school” and “new school” chemo has resulted in better outcomes, but, according to Dr. Mikhael, there is more to come…much more!

Dr. Kyle reminded the audience that there are no established front-line or second-line therapies for WM, and few prospective randomized studies have been done to determine what the most appropriate such therapies might be. Drugs that are used for front-line therapies may also be used in the context of relapsed/refractory disease. The challenge is to recognize on Day 1 how a patient will respond to a therapy – a challenge we have not yet been able to meet.

Dr. Kyle discussed the treatments most frequently used at Mayo Clinic. Patients with mild symptoms of one or more of the following – hemoglobin 10-11 g/dL, platelets 100,000-200,000, severe IgM-related neuropathy, WM-associated hemolytic anemia – are treated with one 4-week cycle of single-agent rituximab. Patients with more pronounced symptoms of one or more of the following – bulky disease (enlarged lymph nodes or spleen), hemoglobin less than 10 g/dL, platelets less than 100,000, constitutional symptoms (fever, weight loss, night sweats, fatigue), symptomatic hyperviscosity – can be treated with two slightly different pathways. The patient with symptomatic hyperviscosity should receive plasmapheresis before beginning therapy with combination dexamethasone, rituximab, and cyclophosphamide (DRC), while patients without hyperviscosity can proceed directly to the DRC regimen.

Dr. Kyle also briefly outlined the advantages and disadvantages of using rituximab. Rituximab is a monoclonal antibody that targets the CD20 antigen on the surface of B-cells, including WM cells. The response to rituximab is variable, in the range of 30-60%. About half of patients who receive rituximab will experience a temporary “flare” (increase) in the IgM. This does not signify treatment failure, and in fact, there are frequently delayed responses of 6-12 months. The duration of response is also variable, ranging from months to years. The use of rituximab with chemotherapy generally increases overall response rates to approximately 60-90%. Mayo Clinic does not recommend the use of maintenance rituximab for several reasons, which include the following possible side effects and disadvantages:

- Late onset neutropenia (decreased neutrophils)
- Late onset anemia
- Doubled risk of infections
- Interstitial lung disease
- Progressive multifocal leukoencephalopathy (a neurological disorder caused by viral reactivation)
- Activation of hepatitis B or hepatitis C
- No proven overall survival benefit
- Potential development of disease resistance
- Inconvenience
- Cost

Combination therapies may be considered according to whether or not they are toxic to stem cells. This is important for patients who may be considering stem cell banking or autologous stem cell transplant, which Mayo considers to be an under-utilized treatment option in relapsed WM.

Combinations that are not toxic to stem cells include DRC (dexamethasone + rituximab + cyclophosphamide) with a reported overall response rate of 83%; BDR (bortezomib + dexamethasone + rituximab) with a reported overall response rate of 96%; and thalidomide + rituximab + dexamethasone. The BDR regimen with bortezomib administered twice weekly resulted in peripheral neuropathy in 69% of patients; consequently, another bortezomib combination regimen using bortezomib once weekly with rituximab had a response rate of 81% but with less neuropathy. The thalidomide combination is used more commonly in Europe than in the U.S.

Treatments that are toxic to stem cells include fludarabine + rituximab with a reported response rate of 95%; FCR (fludarabine + cyclophosphamide + rituximab) with a response rate of 79%; cladribine + rituximab with a response rate of 90%; and bendamustine + rituximab with a response rate of 90%. Dr. Kyle noted that most of these treatments have side effects which include severe neutropenia (reduction in neutrophils) and thrombocytopenia (reduction in platelets). The fludarabine and cladribine regimens also carry an increased risk for the development of myelodysplasia/acute myeloid leukemia and for transformation to a more aggressive lymphoma such as diffuse large B-cell lymphoma.
Chlorambucil is an older treatment which is active in WM and results in response rates of about 60-70%, but is slower-acting and carries with it an increased risk for developing myelodysplasia/acute myeloid leukemia.

Dr. Kyle listed several novel drugs which are either available now or may be in the near future. These include everolimus (RAD001) with a response rate of 70%, perifosine with a response rate of 35%, alemtuzumab (Campath) with a response rate of 75%, and panobinostat with a response rate of 22%. Dr. Kyle note that alemtuzumab, while effective, has resulted in severe cytopenias (reduced blood counts), rash, and infections.

The role of transplantation in relapsed WM was also discussed. A European study on autologous stem cell transplants reported that after 5 years of follow-up, the progression-free survival was 40%, overall survival was 66%, and the relapse rate was 52%. Dr. Kyle pointed out that allogeneic transplantation is rarely used in WM.

Dr. Kyle expanded his discussion of survival rates to note that some of the overall survival statistics may seem somewhat disappointing, but that these statistics also include death from causes other than WM. The WM patient population is an older one, and the risk of death from cardiovascular issues and other cancers may become even more of a risk factor than WM as we age.

For those who might be interested in participating in clinical trials, Dr. Kyle suggested searching the website www.clinicaltrials.gov

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PROGRESS IN NEWER ANTI-CD20 ANTIBODIES

Dr. Maloney’s presentation began with a discussion about antibodies and how they protect the body and target antigens, which are the molecules on a “foreign” body that an antibody is programmed to attack. Tumor cells, being part of our own bodies, are not normally the targets of antibodies created by our own B-cells. But some of the most effective treatments for cancer involve special antibodies, called monoclonal antibodies or MABs, designed in the lab to attack tumors by attaching themselves to a certain target antigen that is expressed on the surface of the tumor cells. One of the most successful in this class of treatments is rituximab, and the antigen on the surface of a Waldenstrom’s cell targeted by rituximab is called CD20.

Some of the characteristics of an appropriate antigen on a tumor cell that make it suitable for targeting by a monoclonal antibody include the following:

- It is always present on the tumor cell
- It is always the same with no variation
- It is required for tumor cell survival so that the cell can’t live without it
- It is expressed on all tumor cells
- It is not present on critical non-tumor cells
- It is not shed, changed, or secreted after the antibody binds to it

CD20 is a target antigen that is present on the surface of B-lymphocytes. It is expressed on most mature normal and malignant B-cells and is not present on early progenitor cells or plasma cells. This means that antibody treatment against the CD20 antigen targets mature normal and malignant B-cells, but the stem cells and other progenitor cells will be unaffected and will reproduce new normal B-cells. CD20 is very stable and does not shed, change, or move from the surface inside the cell. Tumor cells causing chronic lymphocytic leukemia (CLL) and several kinds of B-cell lymphomas also express CD20, so we have been able to borrow treatments for WM that were developed for these more common cancers.

Monoclonal antibodies like rituximab are engineered in the laboratory; they are cloned from antibodies in living organisms, frequently mice. They can be fully human, fully murine (mouse), or chimeric, meaning part mouse and part human. Rituximab is chimeric, and the so-called humanized MABs are especially modified chimeric ones. Some patients react to rituximab because their own antibodies attack the mouse part of rituximab. This situation has accordingly led to the creation of fully human monoclonal antibodies.

Dr. Maloney said that researchers don’t fully understand how these monoclonal antibodies work. One possible mechanism is Antibody Dependent Cell Mediated Cytotoxicity (ADCC). In this mechanism, the other end of the antibody – the part that does not bind to the antigen – binds with natural killer (NK) cells of the patient’s own immune system, which then attack and kill the tumor cell. Another mechanism is Complement Dependent Cytotoxicity (CDC), wherein a system of protein molecules called complement, which is present in the blood, is activated by the antibody and forms pores in the tumor cell membrane, eventually killing it. A perhaps better and more direct mechanism is Apoptosis and Growth Signal Blockade, wherein the antibody itself, without assistance from the patient’s immune system, can cause the cell to fragment and die. Efforts are underway to make antibodies that have this third function.

Rituximab has been the most successful of the targeted MABs so far. It is well tolerated, which makes it especially...
useful for elderly patients. It works better on patients who have not been extensively treated previously and provides a median response of about 2.5 years as monotherapy (single agent therapy) for WM patients in a schedule of four weekly treatments.

Some patients may profit from extended therapy or from maintenance therapy with rituximab. Extended therapy consists of four initial weekly treatments with rituximab followed by four additional treatments during weeks 12-16. Several maintenance therapy schedules have been used, but there have been no randomized clinical trials that measure the effect of maintenance therapy on the survival rate in WM patients. There are studies to suggest that the time to disease progression is extended by maintenance therapy; however, there are also some side effects, including prolonged B-cell depletion, low IgG, and infections. Therefore, the decision about maintenance therapy should be made with care.

Dr. Maloney said it is likely that rituximab works through the ADCC mechanism, which depends on the effectiveness of patients’ own immune cells. But patients vary, and some patients’ immune systems work better with rituximab than others. Research has found that the genetic makeup of some people allows their natural killer cells to bind more effectively to rituximab – these people have “high affinity receptors” – while other people have a genetic makeup that makes binding less effective. There is some ongoing research to modify the rituximab antibody to make it more effective in patients who lack the high affinity receptors.

Another characteristic of rituximab treatment is the “flare,” – or high spike in IgM experienced by many WM patients – that can cause an increase in viscosity, neuropathy, or cryoglobulins levels after treatment begins. There are now some modified protocols for rituximab treatment that minimize the adverse effects of flare. Flare is less frequent when rituximab is combined with chemotherapy drugs.

Rituximab can be combined with chemotherapy, and many different agents have been used to enhance the effectiveness that either rituximab or the chemo would have by itself. Most treatment therapies for WM are used in this way, and better overall response rates and depth of remissions have been reported with combination therapy.

There are many efforts ongoing to make a “better rituximab.” The following are some of the candidates that are being tested in clinical trials:

- ofatumumab – exhibits greater CDC activity at lower CD20 density
- GA-101 – a type II antibody with greater ADCC and direct killing effects
- veltuzumab – a humanized MAB with similar activity to rituximab
- ocrelizumab – a humanized MAB
- AME-133 – better binding to low affinity receptor cells
- PRO131921 – an engineered humanized MAB with greater ADCC activity and better binding to low affinity receptor cells
- ublituximab – a chimeric antibody with greater ADCC activity

To date most of the above have not been FDA approved because, although they are effective, they have not been shown to be better than rituximab, the current best treatment. They all look better than rituximab in the laboratory, but human trials are expensive, and the evidence has not been compelling enough to the drug companies to aggressively pursue FDA approval for many of these.

There are, however, two CD20 MABs which either have been approved or are close to being approved for certain B-cell malignancies.

Ofatumumab, mentioned above, binds to a different part of the CD20 molecule and has shown good progress in non-randomized trials. It can be used if a patient has become refractory to prior rituximab therapy. It is potent in the lysis of B-cells and is more effective for CDC activity than rituximab. It is also effective for tumor cells with low CD20 expression, which includes CLL cells; it has demonstrated activity in refractory CLL and was FDA approved for this indication.

Most of the monoclonal antibodies described above, including rituximab, are Type I antibodies. A newer antibody mentioned above, called GA-101, is a Type II antibody. Type II antibodies have more direct killing power against tumor cells. In preclinical studies comparing it to rituximab, GA-101 showed increased direct cell death induction and enhanced ADCC. A study of GA-101 in WM patients reported similar results. GA-101 is being evaluated in an extensive clinical trial program for B-cell malignancies, particularly follicular lymphoma; preliminary results show an overall response rate better than rituximab, but it has not improved the time to disease progression.

Dr. Maloney concluded his presentation with the following points:

Rituximab is a standard and active treatment for WM in monotherapy, extended schedule therapy, and maintenance. It is included in most front-line treatment regimens with improvements in the depth of response. More improvement is needed. Very few patients achieve complete remission with rituximab. Little is known about monoclonal antibody kinetics in WM, and there is likely room for dose escalation.

Newer antibodies (ofatumumab, GA-101) are better in the laboratory but need direct comparison to rituximab in the clinical setting. They have greater ADCC and greater direct anti-tumor effects but have not been shown in randomized trials to be better in the long term.
Hematopoietic stem cells are the cells that produce virtually all the mature cells of the bone marrow. They have the surface marker CD34, are capable of self-renewal, and have the potential to differentiate into multiple different kinds of blood cells. These characteristics of hematopoietic stem cells have led to the development of two major types of stem cell transplants: autologous and allogeneic.

Autologous transplants have the following characteristics:

- They use the patient’s own stem cells.
- Their purpose is to “rescue” the bone marrow following chemotherapy and/or radiation that is lethal to the marrow.
- They are well-tolerated with a low mortality rate (less than 5%).
- Engraftment, or production of new blood cells, takes place within 10-14 days of transplant.

Allogeneic transplants differ in some important respects:

- They use a donor’s stem cells (donor may be related, unrelated, or umbilical cord blood).
- There are myeloablative or non-myeloablative in nature (see explanation below).

Hematopoietic stem cells can be collected from the peripheral blood after mobilizing them into the blood from the bone marrow with chemotherapy and/or growth factors. Stem cells collected in this way tend to engraft more rapidly and are more cost-effective to collect. Stem cells can alternatively be collected from the bone marrow itself, although this is generally used now only if peripheral stem cell collection fails or in the case of pediatric transplants. Stem cells can also be collected from umbilical cord blood, although this collection method is used more often in children than adults.

The typical autologous transplant is an involved procedure. First, the patient must have an extensive history and physical, including an infectious disease workup, pulmonary function tests, an EKG, a chest X-ray, creatinine clearance test, and an echocardiogram. These are necessary to be reasonably certain that a patient can withstand the rigors of transplant. Once the transplant is approved, the patient’s stem cells are mobilized into the peripheral blood and collected by apheresis. At this point, the stem cells are frozen in a special preservative called DMSO and can be stored that way for many years. Some patients may elect to just harvest their stem cells for future use or they may proceed directly to transplant. Once the stem cells are safely collected, the patient is given a conditioning regimen, which is chemotherapy that is high dose and specific for the disease. After the conditioning regimen, the patient’s blood counts will decrease until virtually all the bone marrow is eradicated. During and after this period, the patient receives supportive care in the form of pain and nausea control, anti-fungal, anti-bacterial, and anti-viral prophylaxis, and close monitoring for the presence of infection or other side effects. In about a week, the patient receives the actual transplant of his stem cells in a slow infusion. During this time, he or she is closely watched for any side effects from the DMSO preservative. Engraftment (production of new blood cells) usually begins 10-14 days following transplant. Long-term follow-up is necessary in order to minimize any complications from the procedure. The most common side effects that occur during the transplant process include fatigue, nausea/vomiting/diarrhea, mucositis (mouth sores), myelosuppression (bone marrow suppression), and organ toxicity to the heart, liver, lungs, and kidneys.

Given that a transplant can be a rigorous procedure, why would a patient with WM consider one? The primary reason is that it can prolong the time to disease progression. Many studies in multiple myeloma and non-Hodgkin’s lymphoma have corroborated this result. Dr. Sherwood related his personal experience with an autologous transplant in 2006. Prior to this, he had received multiple treatments following his diagnosis; he would have a good response to each treatment but he quickly relapsed. His transplant has allowed him to get off the treatment “roller coaster” and enjoy a better quality of life for several years.

The procedure for an allogeneic transplant is much like that for autologous, except that the stem cell donor is also required to have a workup, which includes HLA typing to see how compatible his stem cells will be with the recipient’s. The closer the match, the less chance of a complication called graft vs. host disease (GVHD), wherein the donor’s cells see the recipient’s cells as foreign and begin to attack various tissues and organs of the recipient, potentially causing serious problems which may be acute or chronic. Using umbilical cord blood as a source of donor stem cells allows for toleration of a bigger mismatch between donor and recipient without increased GVHD. Umbilical cord blood donation is not frequently used in adults, except when related or unrelated donors that are a good match cannot be found.

As mentioned above, there are two types of allogeneic transplants: myeloablative and non-myeloablative. Myeloablative transplants use high dose chemotherapy and/or radiation that eradicates the recipient’s bone marrow,
while non-myeloablative transplants use lower doses of chemotherapy and/or radiation that suppress the recipient’s immune system enough to allow the donor cells to move in and take over.

One advantage of an allogeneic transplant is an effect called graft vs. disease. In this case, the donor’s cells, especially the T-cells and natural killer cells, will kill any residual tumor cells in the recipient. At this point, the graft vs. disease effect probably offers the best hope for a “cure” in WM.

Dr. Sherwood cautioned that long-term transplant survivors may continue to have secondary risks associated with the procedure – these can include a higher rate of new cancers and cardiac complications. He also strongly suggested that patients who are candidates for autologous transplant or for stem cell harvest should avoid prior treatment with agents that might interfere with stem cell collection. These agents include most alkylators (with the exception of cyclophosphamide) and nucleoside analogs.

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**NOVEL THERAPIES FOR INDOLENT LYMPHOMAS**

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There are several emerging therapies for indolent (slow-growing) lymphomas that show potential for the treatment of WM. Dr. Advani grouped these therapies into classes, according to their mode of action, and described several of the more promising therapies in each class.

**Antibody Drug Conjugates (ADCs)**

These are monoclonal antibodies to which a potent cytotoxic (cell-killing) drug is conjugated or attached. ADCs result in a more targeted delivery of potent tumor-killing agents to cancer cells by means of specific cell surface antigens found on the cancer cells. They have advantages because they reduce the exposure of normal tissue to the cytotoxic drugs and thus allow for increased dosing to the cancer cell.

The two monoclonal antibody B-cell targets for ADCs currently being tested in clinical trials are CD22 and CD79b. Both are expressed in 90% of B-cell non-Hodgkin’s lymphomas and are internalized, or brought inside the cell, upon binding with the antibody. This means that the cytotoxic drug attached to the antibody is also brought inside the cell, allowing for a more efficient and targeted killing mechanism.

One of the cytotoxic drugs used with both CD22 and CD79b monoclonal antibodies in clinical trials is called MMAE. In most patients it appears to be well tolerated although it does cause peripheral neuropathy in about 15%. In trials, the drug appears to be clinically active in both follicular lymphoma and diffuse large B-cell lymphoma. It has not yet been tried in WM.

Calicheamicin is another cytotoxic agent that can be attached to the CD22 monoclonal antibody. This drug has resulted in a 68% response rate in indolent lymphoma, and its main toxicities are decreased platelets and decreased white blood cell counts. Adding rituximab to this particular ADC has resulted in many complete responses (absence of disease markers) in follicular lymphoma patients.

**Agents Targeting Intracellular Survival Pathways**

These types of drugs turn off the machinery inside the tumor cells which keeps them alive. The most prominent of these drugs are the BCL-2 inhibitors, NF kappa B inhibitors, and HDAC (histone deacetylase) inhibitors.

The BCL-2 inhibitor currently further along in testing is called ABT-199. It is reasonably well tolerated, and in a clinical trial which included several types of indolent lymphoma, the WM patients enrolled had a partial response to the drug.

The drugs targeting the NF kappa B pathway include the proteasome inhibitors. Many of us are already familiar with bortezomib (Velcade), and the newest drug in this same class is carfilzomib. Combining carfilzomib with rituximab and dexamethasone (CaRD therapy) has resulted in an overall response rate of 80% in WM patients, with minimal neuropathy.

The HDAC inhibitor which has been tested in WM patients is panobinostat. It is a clinically active agent but has caused decreases in platelet counts and in WBC counts.

**Agents Targeting the B-Cell Receptor and Its Signaling Pathways**

The B-cell receptor is critical for normal B-cell maturation and survival. Its pathway is a complex one – Dr. Advani described it as a “spider web” with many interconnections – and involves several potential downstream targets, among them BTK, PI3 kinase, mTor, and Akt.

The BTK inhibitor ibrutinib is probably the most exciting new development in WM right now, following closely on the heels of the discovery of the MYD88 L265P mutation in most patients. BTK (Bruton’s tyrosine kinase) was discovered by a pediatrician with the last name of Bruton in Washington DC. As Dr. Advani pointed out, the MYD88 L265P mutation induces BTK activity, thus making ibrutinib a particularly interesting treatment choice for those with the mutation. Dr. Advani was involved in an early Phase I trial of ibrutinib, which resulted in an overall response rate.
of 85%. The most common toxicities, most of which were mild, included diarrhea, fatigue, and nausea. Dr. Advani shared unpublished preliminary results from a Phase II multi-center trial of ibrutinib in 35 relapsed/refractory WM patients [editor’s note: these results were just recently announced at the International Conference on Malignant Lymphoma in Lugano, Switzerland]. In this trial, three pills a day were taken in six monthly cycles. The median time to first response took two cycles, and side effects included thrombocytopenia (decreased platelets), neutropenia (decreased neutrophils), and nosebleeds. Significant responses were seen in approximately 57% of patients. Additional patients have now been enrolled in this study.

Dr. Advani relayed an interesting anecdote about one of the patients in the Phase II ibrutinib study with nosebleeds who had also been taking a fish oil supplement. When Dr. Advani researched fish oil, she discovered that it can have an adverse effect on platelet function; consequently, the patient discontinued fish oil and his nosebleeds ceased. Dr. Advani used this anecdote as a reminder that side effects do not always occur because of treatment and that it is important for patients to communicate to their doctors all the supplements and other medications they are taking.

GS-1101 (also known as idelalisib and CAL-101) is an oral PI3 kinase inhibitor that has been used for both non-Hodgkin’s lymphoma and chronic lymphocytic leukemia patients. It results in more hematologic toxicity than ibrutinib, as well as pneumonia and abnormal liver function test results.

Everolimus (RAD001) inhibits the mTOR part of the pathway. The drug has achieved an overall response rate of 72% in WM patients. Toxicities include myelosuppression (suppression of the bone marrow) and pneumonitis.

Perifosine, which targets Akt, has an overall response rate of 35% in WM.

Dr. Advani summed up by saying that many exciting new agents are available, but the challenge is to develop rational combinations of these and other drugs with the goal of individualizing therapies. To this end, it is important for patients to join clinical trials and increase the potential for discovering a cure.

Dr. Hardy defined integrative oncology as the maintenance of maximum wellness at any stage of the cancer journey by facilitating cancer treatment and the recovery process with the use of integrated complementary therapeutic options. Dr. Hardy views cancer care as a continuum, beginning with prevention and risk reduction and then the use of appropriate screening and diagnosis tools. Finally, if cancer is found, it is important to choose the right level of treatment and follow-up during the recovery period. Dr. Hardy’s views her work as supporting all of these care levels through selection of appropriate diet, exercise, and supplementation. This care includes both the patient and the often forgotten caregiver.

We hear advice throughout our lifetimes on diet, exercise, and “miraculous” supplements. Dr. Hardy says that the problem, particularly for those suffering from cancer, is that we are bombarded with too many choices. Some of them, especially those found on the Internet, can be unreliable, biased, inaccurate, and designed to prey on the desperate. She urged everyone to find a competent advisor when selecting any course of action. This may include friends and family, who are sure to offer well meaning advice, but should also include reliable experts such as your health care provider, pharmacist, or a specialist in complementary alternative medicine (CAM) who is also savvy about conventional medicine.

Ultimately, patients must consider risks, benefits, and costs, both in terms of dollars and in the amount of interference CAM creates with daily life. The most common targets for CAM use include treatment side effects, menopausal symptoms, fatigue, weight loss, insomnia, neuropathy, “aches and pains,” and mood issues. The most common therapies to utilize include nutrition, dietary supplements, herbs, exercise, yoga, relaxation strategies, psychosocial support, and acupuncture.

Dr. Hardy addressed exercise. First and foremost, she stressed that a diagnosis of cancer should not be considered an excuse for not exercising. Exercise at some level is good for almost everybody. Aerobic exercise is good for cardiac health and
for combating feelings of fatigue or depression. Yoga and tai chi are also good exercises for fatigue or depression. Weight bearing and resistance exercises are typically used for bone health but will also aid in muscle preservation. For any exercise plan, it is important to select a reasonable goal, start slowly, and proceed safely. Finding a trainer or training partner can help greatly in developing and sticking to an exercise plan that is appropriate for the patient.

The optimal diet choice will likely be centered on the prevention of inflammation. This includes complex carbohydrates (vegetables and fruits) with low glycemic index, balanced with a healthy portion of “good” proteins (cold water fish and beans) and “good” plant-based fats. Saturated fats, generally from animals, should be avoided as should animal protein, especially from red meats. Sugary foods should also be avoided since they can cause your body to produce insulin, which is known to help grow many types of cancer cells. Total caloric input should also be limited to help avoid growing excess fatty tissues which, in effect, encourage insulin production. Excessive alcoholic input should also be avoided because processing it is difficult for our bodies.

Dr. Hardy published a paper in 2008 which summarized a number of supplements that can significantly reduce symptoms during active cancer treatment with little or no apparent interference (Hematology Oncology Clin N Am, 2008, 581-617). Those mentioned included ginger for nausea; fish oil for cancer related weight loss and muscle atrophy; glutamine for neuropathy and mouth sores; melatonin for neurotoxicity, bone marrow problems, and insomnia; medicinal mushrooms for the general improvement in quality of life; calendula homeopathic cream for skin issues associated with radiation; flavonoid-rich plants for lymphedema; black cohosh for menopausal symptoms; and carnitine for chemotherapy- and radiation-related fatigue.

Dr. Hardy highlighted fish oil, vitamin D, and curcumin as potential every-day supplements to consider. Fish oil contains ingredients that fight inflammation. Vitamin D increases cell differentiation and apoptosis (cell death) while decreasing proliferation and angiogenesis (increased blood vessel development). It is also helps strengthen the immune system. Most people are deficient in Vitamin D, a molecule manufactured by our bodies when exposed to UV light. UV light is avoided owing to concerns related to skin cancer, so supplementation is usually needed to obtain appropriate amounts of Vitamin D. Curcumin has many benefits, helping to inhibit carcinogenesis, decreasing urinary protein, beta-2 microglobulin, and creatine, and also helping to prevent bone marrow breakdown. Dr. Hardy thought curcumin might be an important supplement, in particular, for those with the smoldering forms of WM.

When choosing nutritional supplements, there are many potential red flags that patients and their caregivers should look for. Supplements that are too good to be true usually are. Beware of supplements that overpromise good results, include secret ingredients or formulas, or are very expensive, especially if the seller is unwilling to discuss the product with medical peers, only provides anecdotal evidence, dismisses the possibility of a harmful reaction, or is very critical or dismissive of traditional medicine or medical systems. Ineffective or even toxic products that Dr. Hardy mentioned include laetrile, amygdalin, Vitamin B17, and cyanogenic glycoside from Prunus sp.

Dr. Hardy warned that “natural” does not always mean safe. Use of the words “standardized,” “verified,” or “certified” in the advertisement does not guarantee product quality. Mislabeling and adulteration can occur such that a supplement may not contain the correct plant species, may contain an amount of active ingredient that is lower or higher than the label states, or may be contaminated with other herbs, pesticides, or metals. The supplement may contain unlabeled ingredients. Thus, choosing appropriate supplements involves selecting quality products from reputable sources and taken with full disclosure to your conventional medical team.

While most approved CAM supplements taken correctly are safe, Dr. Hardy highlighted an extract from green tea, EGCG, as an example of one CAM that has recently been found to interfere with bortezomib (Velcade), a drug widely used to treat myeloma and WM. This underscores the importance of reporting all supplements, even those typically considered safe and beneficial, to your oncologist.

In summarizing, Dr. Hardy stressed that in choosing CAM, we should pick a reasonable goal, discuss options with our oncologists and other skilled professionals, consider risks as well as benefits, integrate the natural therapies into our conventional care, find high quality products and use them at the correct dose, monitor for effectiveness and safety, and don’t lose sight of the larger context of healing. Dr. Hardy encouraged those interested in learning more and discussing CAM in general to visit her website: www.drmaryhardy.com

www.drmaryhardy.com
HOW WM CELLS TALK TO EACH OTHER – THE LANGUAGE OF CYTOKINES

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A web of metabolic pathways is involved in the development of B-cells, which do not exist in isolation but live in a neighborhood of other cells. These cells talk to each other in the language of cytokines. Cytokines are small signaling proteins that act as messengers, allowing cells to communicate. They are secreted in response to stimulation, and they play a role in many cellular responses, including the production of immunoglobulins (antibodies). They often affect the actions of other cytokines. They may travel locally and attach to receptors on WM cells or on other cells in the nearby microenvironment or they may travel through the bloodstream to distant sites. Within the bone marrow, where the B-cells of WM reside, every cell is talking to every other cell through this signaling network. In WM, the “talk” escalates to “gossip,” and some of the normal signaling patterns become distorted.

The Task of the B-Cell

Normal B-cells act in response to signals from their environment to accomplish a specific task: to transform into plasma cells that produce a great variety of immunoglobulins, which can bind to many different foreign antigens, including viruses and bacterial components. As it receives signals from its environment, the B-cell undergoes structural changes that result in its transformation from a lymphocyte to a plasma cell. In stained microscopic smears, the nucleus of a resting mature B-cell takes up most of the cell, and the cytoplasm is pale blue. Plasma cells, on the other hand, have a small, dense, eccentrically placed nucleus and abundant deep blue cytoplasm. The deep blue color of the cytoplasm is due to the presence of many RNA-containing ribosomes, the key component of the protein-manufacturing apparatus that produces immunoglobulins.

In the malignant WM B-cells, the basic task is the same, but the focus has greatly narrowed. Now all of the immunoglobulin-secreting malignant B-cells produce innumerable, identical copies of the same antibody (called monoclonal because they are produced by a single clone of WM cells).

There are two ways in which B-cells respond to encounters with foreign antigens: the B-cell receptor pathway and the Toll-like receptor pathway.

B-Cell Receptor Pathway

When this pathway is activated, a resting B-cell encounters a foreign protein antigen (e.g., from an influenza virus) that is recognized by the surface B-cell receptors. The B-cell internalizes and processes the antigen so that a fragment of it is combined with an HLA (human leukocyte antigen) class II molecule within the cytoplasm. The resulting complex is presented on the B-cell’s surface, where contact with a T-helper cell occurs. If the surface receptors of the T-cell recognize the antigen/HLA complex, it secretes cytokines that result in activation of the B-cell. An activated B-cell undergoes clonal proliferation (i.e., all of the daughter cells are identical), and some of the clonal progeny become antibody-producing plasma cells. Long-lived plasma cells are generated via the slower BCR pathway. Short-lived, predominantly IgM-secreting plasma cells are generated via the rapid TLR pathway (see below).

Toll-Like Receptor Pathway

Another pathway through which the B-cell responds to foreign antigen is via the Toll-like receptor (TLR), the “quick and dirty” pathway, meaning that these antibodies (typically IgM) are produced more rapidly but lack the specificity of the B-cell receptor pathway. Antibodies produced in this way have weaker affinity for their antigens and are generally less effective than those generated by the BCR pathway. A key component in this pathway is the protein MYD88, produced by the MYD88 gene (see below). The TLR pathway does not respond to all types of antigens; instead, it responds to molecules that are shared by a variety of different pathogenic organisms. B-cell activation by this pathway is followed by differentiation into short-lived plasma cells that produce predominantly IgM antibodies. Contact with a T-cell is not required. This less specific response provides an early defense against infection with pathogenic organisms until the T-cell-dependent BCR pathway has had time to develop and produce its antibodies.

The End Result of B-Cell Differentiation to a Plasma Cell

Various types of immunoglobulin (abbreviated Ig) are produced and secreted: predominantly IgG in the BCR pathway and predominantly IgM in the TLR pathway. IgA is found in association with mucous membranes and in the bowel, whereas IgD and IgE are associated with allergic responses. Basic immunoglobulin molecules are Y-shaped and consist of two longer heavy chains, each of a type specific for the particular class of immunoglobulin, attached to two shorter light chains that are confined to the branched “arms” of the Y. The antigen-binding end is the branched end of the molecule.

- IgG, the most prevalent immunoglobulin under normal circumstances, is a monomer (consisting of one copy) of the Y-shaped basic structure just mentioned.
• IgA, the next most common immunoglobulin, exists as a dimer (consisting of two joined copies).
• IgM, the next most common immunoglobulin under normal circumstances, is a pentamer (consisting of five copies) of the basic Y structure that is joined in a rounded aggregate in which the branched “arms” are all pointing outward.
• IgD and IgE are monomers that are present in very small amounts.

**What Has Gone Wrong in WM?**

**Excess monoclonal IgM protein** results in hyperviscosity and sometimes neuropathy. In the normal state, antibody production is well controlled. In WM, IgM production is poorly controlled, and very high blood levels of IgM can result. The large size of the IgM molecule contributes to the hyperviscosity symptoms associated with WM.

**Lymphoplasmacytic lymphoma in the bone marrow** is characterized by a range of cells from small B-cells to plasma cells. Under normal circumstances, proliferation of B-cells is well controlled. Activated B-cells and plasma cells and the antibodies that they produce would be relatively abundant immediately after an infection, then would return to the normal resting phase levels within a few weeks. In WM, however, the cells continue to proliferate and produce IgM. This cellular expansion occurs within the bone marrow, often accompanied by anemia as normal red cell-producing cells are crowded out. It sometimes also occurs outside the marrow (extramedullary expansion), which may give rise to enlargement of the spleen and lymph nodes.

**Cytokines Are Elevated in WM**

Cytokines are produced by WM cells, normal B-cells, T-cells, macrophages, endothelial cells (that line blood vessels), and stromal cells (bone marrow connective tissue cells in the environment around the WM cells). There is too much cytokine traffic (“gossip” or “chatter”) in WM, and there are substantial differences in the levels of different cytokines in the blood between WM patients and normal control individuals. Some cytokines are increased and some are decreased. Protein production is said to be dysregulated. Following are several cytokines that are important in WM:

**BLyS (BAFF)** is critical for maintaining normal B-cells and for immunoglobulin production. Too little results in absence of B-cells and low immunoglobulin levels. In WM, BLyS is produced both by WM cells and other cells in the environment under the influence of WM cells. In the blood of WM patients, BLyS levels are increased (relative to normal controls). It collaborates with other cytokines, including IL-6 and IL-21, to increase IgM production in WM cells.

**IL-6** expression is increased in WM. IL-6 is an inflammatory cytokine that causes B-cell proliferation and differentiation and stimulates T-cell proliferation. When WM cells of patients are treated experimentally with increasing doses of IL-6, increasing amounts of IgM are produced. The more IL-6 that a patient produces, the more IgM will be produced. IL-6 is controlled by a different cytokine – CCL5 (also known as RANTES).

**IL-21** expression is increased in WM. IL-21 also collaborates with BLyS and IL-6 in making IgM. IL-21 is made by T-cells and natural killer cells. It promotes plasma cell differentiation and proliferation, prevents WM cell death (apoptosis), and controls IL-6 production.

There are several genes that need to be activated in order for a B-cell to transform into a plasma cell, and IL-21 drives the activation of those genes. When WM cells are treated with IL-21, there is increased production of a variety of other cytokines, including IL-6 and IL-10. There is a feedback loop in which one cytokine stimulates another, and that cytokine in turn further stimulates the first cytokine, part of the “chatter” referred to above.

**CCL5 (RANTES)** controls IL-6 in WM. Of all of the cytokines that Dr. Ansell has studied in WM, CCL5 is present in the highest levels. It is made by the WM cells and it stimulates the stromal cells, thereby influencing the bone marrow microenvironment of WM. CCL5 signaling is transmitted via the intracellular protein GLI2. CCL5 stimulates the stromal cells to make IL-6, which, as noted above, drives proliferation of WM cells and IgM production via the JAK/STAT pathway.

**MYD88** mutations amplify the “gossip” of certain cytokines. MYD88 plays a role in the BCR signaling pathway and the Toll-like receptor pathway. When activated, the TLR pathway drives cytokines via the JAK/STAT pathway. The MYD88 mutation acts rather like a megaphone, producing a greatly amplified signal that drives WM cells to produce more IgM.

**Summary**

- WM is a disease with two problems – the cancerous cells in the bone marrow and lymph nodes and the IgM protein in the blood.
- There is back and forth communication between the malignant B-cells and the microenvironment.
- Cytokines made by cells in the tumor microenvironment support the growth of the cancer cell and the production of IgM. IgM production is controlled by cytokines including BLyS, IL-6, IL-21, and CCL5. It is likely that additional cytokines will be found to play a role in this disease.
- Interfering with this control of cellular proliferation and IgM production may be a future treatment option.
We inherit traits such as eye color from our parents through DNA (deoxyribonucleic acid). DNA may be viewed as a blueprint that encodes instructions for the regulation of cell function. Differences in these instructions account for most inherited traits. Damage to DNA can alter these instructions, which causes the affected cells to change their behavior—and some changes in cell behavior can result in disease, including cancer.

Human DNA is organized into 23 chromosomes. Each person has two copies of each chromosome, one from each parent. The DNA in these chromosomes is made of complex molecules called nucleotides. The four types of nucleotides are abbreviated A, T, C, and G. Nucleotide bases form stable pairs: A bonds with T and C bonds with G. Such bonded base pairs are said to be complementary. Genes are sections of these complementary base pairs that contain instructions on how to build proteins. In the cell nucleus, genes in the DNA are transcribed into single strands of similar nucleotides called messenger ribonucleic acid (RNA). The messenger RNA travels from the nucleus into the cytoplasm, where the "messages" carried by the RNA are translated into proteins that affect cellular function.

Although the flow of information goes predominantly from DNA to RNA to protein, there is a lot of back-and-forth talk. Proteins can go back to the nucleus and modify gene expression (whether a gene is transcribed or not), and RNA can modify other RNA molecules and proteins.

Why Is the Study of Genetics Important in WM?

The study of family inheritance in WM has implications for treatment response and patient care and allows us to gain a better understanding of predisposing disease factors so that we can try to mitigate them. The analysis of cancer-specific genetics tells us several important things:

- It documents changes in the DNA blueprint.
- It enables us to study how those changes lead to the development of WM and its progression.
- It allows us to find new targets such as MYD88 in order to create new, more precise therapies.
- It helps us to develop prognostic criteria that predict how aggressive or indolent the disease may be.
- It may predict response to therapy and allow for individualized treatment plans.

Familial WM

While reviewing the family trees of patients in a familial WM study, the Bing Center group at DFCI noticed three broad categories that could be used to classify the families.

- Familial WM: multiple cases of WM were observed
- Familial Mixed B-Cell: multiple B-cell cancers were observed, but only one case of WM
- Sporadic WM: no other B-cell cancers were observed in the family

The Bing Center looked at 924 consecutive WM patients, and it was seen that 27.5% of patients had a history of some kind of familial disease. Only about 5% had a history that was specific for WM. By using family histories and looking at the clinical situation of WM patients, researchers were able to draw some important conclusions:

Progression-free survival (PFS) and time to next treatment (TNT) are associated with familial disease status. A study of 159 patients treated with rituximab-based therapy (without bortezomib) revealed that patients in the Familial WM and Familial Mixed B-Cell groups had shortened PFS and TNT in comparison to patients in the Sporadic WM group.

Bortezomib Therapy and Familial Disease. When Sporadic WM patients were divided into two groups, one treated with regimens that contained bortezomib and one treated with non-bortezomib regimens, their overall response rates were similar. However, when Familial WM patients were similarly divided into two treatment groups, those treated with bortezomib had substantially better overall response rates than those treated with non-bortezomib regimens. Moreover, the Familial WM patients who were treated with bortezomib regimens had overall response rates comparable to those of patients in the Sporadic WM group. This example illustrates the way in which genetics can play an important role in selecting the most appropriate therapy.

Low IgG and IgA Levels. It was discovered that 9-11% of the individuals without a monoclonal protein within each family group had low IgA or IgG. IgM abnormalities, including IgM MGUS, became progressively more common from the Sporadic WM to the Familial Mixed B-Cell to the Familial WM group.

The Bing Center did a large genetic study in which researchers measured certain parts of the genome that everyone has in common (with minor differences among individuals). More recently, Mr. Hunter and his colleagues at the Bing Center
also performed whole genome sequencing, in which all of the approximately 3 billion bases in the sample DNA were identified. They are combining the genomic data with the familial pedigree data, an ongoing project. So far, the group has studied 55 whole genomes and also has single nucleotide polymorphism (SNP) array results from the family study. By studying individual genes and individual nucleotide variations within the genome, and by tracking family members across generations, Bing Center researchers hope to find areas of the genome that associate strongly with those who have a family history of WM, but not with individuals who do not have a family history.

**The Genetics of the WM Clone**

There is a great deal of genetic heterogeneity in WM. When the lymphoplasmacytic cells of WM patients were tested, mutations in 251 genes were identified. Only 10% of these genes were seen in three or more patients. The median number of affected genes per patient was 26, with a range of 17-36. The following were the most common mutations discovered.

**MYD88 L265P Mutation**

The most prevalent genetic mutation in WM is the MYD88 L265P mutation located in the MYD88 (Myeloid Differentiation Primary Response) gene. This involves a single nucleotide change from T to C (a single nucleotide polymorphism or SNP), which results in an amino acid change in the corresponding protein from leucine to proline at position 265. Proteins are made of amino acids, and when the DNA changes, the corresponding amino acid may also change.

The mutant protein in this case no longer operates properly. Instead of turning on and off in a normal fashion in response to cell signaling, it just gets stuck in the “on” position. Researchers observed this in 27/30 or 90% of the WM patients. This mutation also occurs in some cases of diffuse large B-cell lymphoma (DLBCL), some MALT (mucosa-associated lymphoid tissue) lymphomas, and rarely in chronic lymphocytic leukemia. The mutation has also been found in those IgM MGUS patients who shortly afterward progressed to WM.

A colleague (Lian Xu) in the Bing Center laboratory has developed a very sensitive test for the MYD88 L265P mutation that works on peripheral blood as well as bone marrow. This test is undergoing further evaluation in patients. While it is not yet ready for clinical use, Mr. Hunter anticipates that it will be available in the not too distant future.

**MLL2 Mutation**

The 10% of WM patients who didn’t have the MYD88 L265P mutation were screened for other mutations in the MYD88 gene, and none were found. However, two of these three patients had a mutation in a gene called Mixed Lineage Leukemia 2 (MLL2). Both of these patients had CD23+ WM cells with high levels of CD23+ clonal B-cells circulating in the peripheral blood, both unusual findings in WM. Additional CD23+ WM patients that we have subsequently tested have also been MYD88 negative. This may turn out to be a distinct subtype of WM.

**Chromosome 3 aUPD and Other Structural Variants in WM**

Recall that a child inherits one chromosome from each parent. When a particular gene on a chromosome inherited from one parent has a nucleotide sequence that differs from that inherited from the other parent, the patient is said to be heterozygous for that gene. Acquired uniparental disomy (aUPD) occurs when one of the two gene copies is deleted. The DNA repair mechanism senses that a copy is missing, and replaces the missing copy with another copy of the single remaining gene. When this loss of heterozygosity involves deletion of a normal MYD88 gene, then the WM patient winds up with two copies of the mutant MYD L265P protein. Researchers saw this four times among the WM patients and are currently investigating its significance.

In addition to aUPD, there are a number of other types of structural variants that play a very important role in WM, and these often result in only a single, mutated copy of a gene being present.

**CXCR4 and WHIM Syndrome**

WHIM (Warts, Hypogammaglobulinemia, Infection, and Myelokethexis) Syndrome is a rare autosomal dominant genetic disease (one that is not sex-linked and requires only an abnormal gene inherited from one parent in order to be manifested). This condition causes all of the immune cells to rush to the bone marrow and stay there. In addition, neutrophils are retained in the bone marrow (myelokethexis) instead of migrating into the peripheral blood.

The CXCR4 gene controls the migration and homing of immune cells in the body. It codes for a cell surface receptor protein that has a terminal handle-like structure that extends into the cell cytoplasm. This “handle” allows the receptor to be drawn back into the cell. The cytokine (signaling protein) CXCL12 specifically binds to CXCR4. Once the receptor has engaged with CXCL12, the receptor is retracted within the cell and the homing signal stops. In WHIM syndrome, one end of the receptor protein has been truncated so that the tail or “handle” is missing. As a result, once engaged with CXCL12, the CXCR4 receptor remains on the surface of the cell and continues to signal immune cells to move to the bone marrow.

The Bing Center has seen acquired CXCR4 mutations in WM tumor cells. The cytoplasmic “handle” is missing in these mutations, just as it is in WHIM syndrome. About
27% of WM patients in the Bing study had a CXCR4 mutation.

Copies of these mutations were created in Dr. Treon’s laboratory by Yang Cao, M.D. Using a virus as a vector (an agent used experimentally that delivers genetic material into cells), she infected WM cell lines to make them express three different versions of mutant CXCR4 protein. When exposed to its ligand, SDF-1a (also known as CXCL12, the molecule that the CXCR4 receptor is configured to bind to), one expects the CXCR4 to disappear, or internalize, within the cell. In the cells expressing the normal CXCR4, the CXCR4 receptor disappeared. However, the mutant CXCR4 receptor molecules remained on the cell surfaces, continuing to be expressed. This led to constant activation and signaling of the pathway.

ARID1A and ARID1B Mutations in WM

Due to space constraints, the DNA has to be very compact. The way in which the unwinding of this compacted material occurs as it reproduces affects if and how genes get used. The genes ARID1A and ARID1B are very important in controlling how DNA gets unwound. They accomplish this by adjusting the binding of DNA wrapped around core particles of histone protein (nucleosomes), making some genes more accessible to transcription than others. The Bing researchers observed that about 17% of WM patients had mutations in ARID1A and about 60% had deletions in ARID1B. ARID1B is located on chromosome 6q in an area with significant copy number variation (see Chromosome 6q Structural Variations below.) These data suggest that there is abnormal regulation of the packaging of DNA in WM, and this is currently being studied.

Chromosome 6q Structural Variations

Chromothripsis is an event in which a chromosome is shattered, and its fragments are scattered across all of the other chromosomes. This is a very rare event, and the detection of this in one of the study’s patients prompted researchers to look at deletions in chromosome 6q (the long arm of chromosome 6). A number of these 6q deletions are actually due to translocations, in which a segment of one chromosome is relocated to another chromosome. The Bing group is now investigating whether or not there is any pattern to these translocations, what clinical relevance they have, and how they relate to copy number changes.

Copy Number Changes

Copy number refers to the number of copies of a gene that are located on a chromosome. We have two copies of each chromosome, but there can be more than two copies of a gene. Sometimes a person inherits two copies of a gene from the mother and one from the father, without any adverse effect. However, cancer may also change copy number. For example, if a genetic mutation such as MYD88 L265P occurs that improves the survival of cancer cells, the tumor may make extra copies of that gene. Doing so may help it survive a chemotherapy regimen or make a transition from IgM MGUS to WM.

Looking Toward the Future

In the future, the Bing Center has the following research goals:

- Advance our understanding of the interplay between DNA mutation and RNA transcription.
- Continue to investigate the significance of structural variations at both the gene and chromosome levels.
- Identify genetic signatures to improve prognostic testing and response to individual therapies.
- Characterize what is responsible for the progression from MGUS to WM and search for ways to prevent this progression.
- Identify acquired mutations responsible for resistance to therapy.
- Based on the above, find new drug molecules for improved therapy for WM.

ADVANCES IN WALDENSTRÖM’S MACROGLOBULINEMIA: 2013

STEVEN P. TREON, M.D., PH.D.
Dana-Farber Cancer Institute, Boston, MA

Before Dr. Treon began his discussion of the new genome discoveries and their impact on WM, he presented an overview of the current landscape of WM today – what we have learned and how this information can best be applied to the treatments we are using now.

THE CURRENT LANDSCAPE OF WM

Consensus Recommendations for Initiation of Therapy in WM

As Dr. Treon pointed out, WM is a disease for which watch and wait is appropriate. He discussed the guidelines for when it is appropriate to begin treatment, which include the following:

- Hemoglobin less than or equal to 10 g/dL on the basis of disease
- Platelets < 100,000 mm$^3$ on the basis of disease
• Symptomatic hyperviscosity
• Moderate/severe peripheral neuropathy
• Symptomatic cryoglobulins, cold agglutinins, autoimmune-related events, amyloid

Anemia and Hepcidin
Anemia is the #1 reason for the treatment of WM. Recent discoveries have implicated the hepcidin protein, made by WM and other cells, as important in the prevalence of anemia. Hepcidin reduces iron absorption in the gastrointestinal tract and stimulates the macrophages to “gobble up” extra iron, making it less available to the red blood cells. As hepcidin levels increase, iron deficiency increases. Giving iron intravenously instead of by mouth may help to alleviate the poor absorption in the gut and increase the available iron, thereby possibly prolonging the time before chemotherapy is needed.

Rituximab
An IgM “flare” (temporary IgM increase) occurs in 40-60% of patients receiving rituximab therapy. It is considered prudent to avoid rituximab therapy in patients with an IgM greater than 4,000 mg/dL or with symptomatic hyperviscosity until they have received plasmapheresis or chemotherapy without rituximab and their IgM has returned to a “safe” range. Rituximab can aggravate IgM neuropathy, cryoglobulins, or cold agglutinins, and plasmapheresis should be considered prior to therapy.

Rituximab intolerance is fairly common in WM (about 15% of patients), and consensus guidelines allow for the use of ofatumumab, a different CD20 antibody, in these situations.

Combining rituximab with chemotherapy provides deep remissions (very good partial responses or complete responses) in only 30-40% of WM patients. Dr. Treon emphasized that we need to find better ways to achieve deep remissions.

Nucleoside Analogues (NAs)
Nucleoside analogues (fludarabine, cladribine) carry with them a risk of transformation to a more aggressive lymphoma or to myelodysplasia/acute myeloid leukemia in about 10-15% of WM patients. Stem cell collection after NA therapy may be impacted, and it is recommended to avoid its use in patients who may be future autologous stem cell transplant candidates. One should also carefully consider the prior use of NA therapy in patients who are contemplating bendamustine. The number of therapy courses and the dosing frequency of NAs may need to be adjusted, especially in elderly patients.

Cyclophosphamide-Based Therapy
This type of therapy may be given in combination as CHOP-R, CVP-R, CPR, DRC, etc. Some of these regimens include doxorubicin (H) and vincristine (O, V), which can be fairly toxic. Dr. Treon said that eliminating these two drugs from cyclophosphamide combinations does not appear to impact response rates and progression free survival in WM patients.

Overall response rates with this type of therapy are about 70-90%, with deep responses of 20-25%. The median progression free survival is three years in front-line therapy. Side effects include suppression of blood counts and bladder toxicity. Stem cell collection is not adversely affected, and long-term toxicity risks are modest.

Bendamustine
The combination of bendamustine + rituximab was superior to CHOP-R in front-line therapy for WM in a study conducted by Dr. Mathias Rummel of Germany. It is an excellent option for bulky disease (enlarged lymph nodes, liver, spleen). The dosing should be modified for patients with extensive prior therapies, nucleoside analogue therapy, the elderly, and those with reduced kidney function.

Bendamustine in salvage therapy has a shorter progression free survival than in front-line therapy — about 13 months.

Dr. Treon urged caution with bendamustine use in younger patients since long-term safety remains to be established.

Bortezomib (Velcade)
Several studies have been conducted with bortezomib as primary therapy in WM. One study used bortezomib (1.3 mg/m²) twice weekly + dexamethasone + rituximab and achieved some very good responses. Overall response rate was 95%, with 22% complete responses; however 30% of patients had grade 3 or worse peripheral neuropathy, which was much higher than the rate seen with bortezomib in multiple myeloma. Another study administered bortezomib (1.6 mg/m²) once weekly + rituximab. This study resulted in an overall response rate of 92%, with 8% complete responses. The major improvement was no grade 3 or worse peripheral neuropathy.

Salvage therapy with bortezomib using the once weekly dosing + rituximab has reported an overall response rate of 81%, with 5% complete responses and 5% grade 3 peripheral neuropathy.

Primary Therapy with CaRD
CaRD therapy is based on carfilzomib (an oral proteasome inhibitor in the same class as bortezomib) + rituximab + dexamethasone. Carfilzomib has already been approved for use in relapsed/refractory multiple myeloma. Dr. Treon reported on his new study of CaRD in WM patients. The overall response rate was 75% with only mild (grade 1) neuropathy, and he anticipates that carfilzomib may become an important therapeutic agent in WM.

Maintenance Rituximab
As Dr. Treon said, unfortunately we still don’t have results from randomized prospective studies of maintenance rituximab therapy for WM, although Dr. Rummel from Germany is currently conducting one.

Retrospective studies which look back at patients who have received maintenance rituximab suggest that both progression free survival and overall survival are increased with its use.
Everolimus in Relapsed/Refractory WM

Everolimus is an oral drug which has resulted in overall response rates of 72% and median progression free survival of 22 months. However, IgM discordance has been reported with this treatment, meaning that the IgM shows decreases while the bone marrow infiltration with WM cells does not. The side effects of everolimus therapy include mouth sores, pneumonitis, and grade 3 or greater bone marrow suppression.

NEW DIRECTIONS IN WM

The Genome

Understanding the genome can help us to understand several important concepts in the pathogenesis (disease development) and treatment of WM:

- Predisposition to the disease – some WM patients come from families where the disease is present
- Progression of IgM MGUS to WM
- Progression of smoldering WM to symptomatic WM
- Targeted new drug development
- Personalized approach to therapy
- Understanding resistance to therapy
- Development of animal modeling for drug testing

The MYD88 L265P Mutation

Whole genome sequencing on paired tumor and normal cells in WM patients was responsible for detecting the MYD88 L265P mutation in more than 90% of these patients (see Zachary Hunter’s presentation on “The Genomic Landscape of WM” elsewhere in this publication). The mutation is found in few other diseases, particularly at this prevalence, although it is present in ABC-type diffuse large B-cell lymphoma, primary CNS lymphoma, and a small percentage of chronic lymphocytic leukemia patients. This result has subsequently been confirmed and reported by several researchers worldwide. The mutation has achieved even more importance as we develop more targeted therapies for the disease.

Not everyone with IgM MGUS develops WM, although it has been discovered that at least 50%, and maybe more, of IgM MGUS patients have the MYD88 mutation. Dr. Treon said the search for other mutations that may lead to progression are ongoing in his laboratory, and his hope is that we can eventually target some of these mutations to prevent progression.

Dr. Treon explained the role of MYD88 in cell growth. Every cell has receptors, or ways to receive messages. In the B-cell, so-called Toll receptors sense the presence of infection and activate MYD88, which in turn signals and activates other proteins downstream, the most important of which is the NF kappa B pathway that stimulates the B-cells to grow and survive. When the L265P mutation is present in MYD88, this cell signaling gets stuck in the “on” position, and the cells proliferate and do not die. If the mutation can be silenced, then the tumor cells can be killed. This process has been clearly demonstrated in the laboratory on WM cell lines.

BTK and Ibrutinib

Bruton’s tyrosine kinase is a protein in the downstream pathway of MYD88. Ibrutinib, an oral inhibitor of BTK, caused WM cells with the MYD88 mutation to die; WM cells without the mutation did not die except at very high levels of the drug.

Based on this laboratory work, a multicenter Phase II trial of ibrutinib in relapsed/refractory WM was begun with 35 patients – the trial has since been expanded to 60 patients. Dr. Treon shared some early results from the trial: the median time to first response is two cycles, with decreases in IgM and increases in hematocrit. Approximately 80% of patients have responded, and 33 of the original 35 patients continue on therapy. Toxicities have included thrombocytopenia (decreased platelets), neutropenia (decreased neutrophils), and epistaxis (nosebleeds). Dr. Treon noted that the nosebleeds seem to be associated with the use of fish oil supplements. Ibrutinib has since received Breakthrough Therapy Designation by the FDA for WM, and Dr. Treon hopes it will soon be available in the clinical setting.

Future Plans for Ibrutinib

In future work funded by the IWMF, Dr. Treon and his group will be looking at combining ibrutinib with IRAK inhibitors, which also target parts of the downstream pathway of MYD88, to see if there is any synergy to using the drugs together. Dr. Treon is also looking forward to the generation of a transgenic MYD88 L265P mouse model which will replicate the disease and lead to a better understanding of WM pathogenesis. This model is being developed by Dr. Ruben Carrasco, a colleague of Dr. Treon’s at DFCI, with funding from the Leukemia & Lymphoma Society and WMF Canada.

SUMMARY

Dr. Treon briefly summarized his presentation:

- Bendamustine, bortezomib, and cyclophosphamide-based rituximab therapies are active and can be used in the current management of symptomatic WM patients, with careful consideration of toxicities.
- The use of nucleoside analogues should be carefully considered in WM.
- Maintenance rituximab therapy is associated with improved clinical outcomes in WM.
- Newer options include everolimus, carfilzomib, and ibrutinib.
- The MYD88 L265P mutation is present in more than 90% of WM patients, triggers both the BTK and IRAK pathways, and represents a novel approach for targeted WM therapy.
Dr. Gertz opened with a brief discussion of Dr. Jan Waldenström and how remarkable it was for one man to be solely responsible for recognizing a disease. He was the fourth of five generations of physicians and left quite a legacy in his own right. Dr. Waldenström not only described WM but also other diseases such as porphyria. However, he was also fortunate during this time to be able to collaborate with Dr. Svedberg, who had a new instrument called an ultracentrifuge and using this discovered a “macroglobulin” in the bloodstream of two of Dr. Waldenström’s patients, and with Dr. Tiselius, a biochemist and pioneer in electrophoresis who detected an abnormal protein peak in the electrophoretic pattern of the patients’ serum samples.

Dr. Gertz said that it is sometimes easier to describe what WM is not, rather than what it is – it is not like other non-Hodgkin’s lymphomas, it is not like chronic lymphocytic leukemia with which it has frequently been compared, and it is certainly not multiple myeloma, but it is a very unique entity, with unique surface markers, genetic characteristics, and clinical characteristics.

Dr. Gertz outlined the “good news” about WM:

- It is generally a slow process whose clinical course is many years.
- It is composed of a population of abnormal cells that grow very slowly.
- A high proportion of WM patients are candidates for watch and wait, which is completely appropriate.
- Many patients are detected as a result of improved technology (electrophoresis, automated chemistry profiles) at an earlier stage of the disease.
- In 1979 when Dr. Gertz began practicing at Mayo, the only treatment option was chlorambucil; today we have plasma exchange, fludarabine, cladribine, rituximab, interferon, dexamethasone, thalidomide, stem cell transplantation, cyclophosphamide, ofatumumab, ibrutinib, bendamustine, bortezomib, carfilzomib, lenalidomide, everolimus, and various combinations of the above.

- Knowledge is building quickly; there are approximately nine scientific publications on WM each month, more than 100 researchers whose focus is on the disease, and over 100 active clinical trials open to WMers.
- The IWMF has funded research on WM cell lines, microRNA expression, cytokines, and whole genome sequencing to detect the MYD88 L265P gene mutation and has helped to fund international venues for WM clinicians and scientists to meet and share information on the disease.
- The MYD88 mutation offers a potential target for therapy and potential new monitoring methods.
- There is hope for long-term control of the disease with minimal toxicity.

And Dr. Gertz also explained some of the “bad news” about WM:

- No cure currently exists.
- The availability of so many therapies may result in overtreatment of asymptomatic patients simply because of a “high IgM level.” Dr. Gertz emphasized that the IgM level should not be a determinant for treatment.
- Dr. Gertz and others are seeing many patients without symptoms who have received therapy because newer therapy is “easy.”
- WM remains a rare disorder – Dr. Gertz said there are probably about 40,000 patients in the U.S. with active or smoldering disease and 100,000 practicing oncologists. Thus most oncologists will never see sufficient numbers of patients to really have a “feel” for the disorder and will instead make decisions based on “book learning” – and there is a difference between information and true knowledge of the subject, which is also based on experience. For this reason, patients should not be afraid to ask for a second opinion.

Building on a theme which Dr. Gertz has used in previous Ed Forums, he asked his audience: How does a WM patient help himself or herself tend the garden while the physician is killing the weeds?

Knowledge is power, so educate yourself. The information on WM is often confusing and sometimes anecdotal or hearsay, but any information is likely better than none. Remember, however, that material on the Web is not content-verified. Do not over-interpret statistics because at an individual level they are not very helpful. Even the experts disagree about who has WM, when to treat it, and the role of various therapies.

Have a dialogue with your physician. Physicians should not feel threatened by this, and patients need to be satisfied that they are getting answers to their questions. If this does not happen, choose another physician.

Support research initiatives financially and participate in clinical trials. Funding to the National Institutes of Health has been cut, and researchers are depending on donations.
from the private sector to help. Many patients say they would like to participate in trials but few do. There can be a great deal of satisfaction in doing something that will not only benefit you, but those who will follow you.

Join patient advocacy groups like the IWMF. They can play an enormous role in filtering information for accuracy and can direct patients to the best resources. They frequently have chat lines for patients to exchange information, they sponsor research, and they can provide empathy and experience to other patients.

Pay attention to your lifestyle. Maintain good cardiovascular health and a normal body mass index. Choose a healthy diet by eating a variety of foods with an emphasis on plant sources.

Dr. Gertz cited the American Cancer Guidelines on Nutrition and Physical Activity: eat five or more servings of fruits and vegetables each day; select whole grains instead of refined grains and sugars; limit consumption of red meats, especially those high in fat, and processed meats; and limit consumption of alcohol, which is mostly sugar and adds empty calories to your diet. Adopt a physically active lifestyle and maintain a healthy weight throughout life.

Dr. Gertz closed by mentioning the Mayo Clinic Twitter account, which posts two or three tweets each week with the newest information on WM. The Twitter address is @Waldenstroms.

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