

# *iwmf* bulletin

APRIL 2008

INTERNATIONAL WALDENSTROM'S MACROGLOBULINEMIA FOUNDATION

This special IWMF *Bulletin* is devoted to coverage of our 12th annual Educational Forum held last April in Atlanta. More than 300 attendees had the opportunity to hear from renowned researchers and clinicians with expertise in the study and treatment of Waldenstrom's Macroglobulinemia. Once again we are indebted to IWMF Trustee Jim Berg for summarizing most of the presentations. This year we must also thank Dr. Guy Sherwood and Raquel Lopez for assistance—along with Ron Draftz, who took most of the photos that appear in these pages.

We hope you will join us at our 2008 Educational Forum, which will be held May 16-18 in Los Angeles. Further details and registration information is available on our website, [www.iwmf.com](http://www.iwmf.com).

*Judith May*  
President, IWMF

*–Thriving with WM–*  
**12th Annual Educational Forum**  
**Atlanta, Georgia**

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## **Robert A. Kyle, M.D.**

Mayo Clinic

### *Introduction to Waldenstrom's Macroglobulinemia*

Those of you who are newly diagnosed represent a small part of the population, approximately 1500 persons, who develop the disease in the United States each year. In a country of 300 million, that's not very many.

Our story begins a little more than 60 years ago, when Jan Waldenstrom described the peculiar disease that you have. He called it incipient myelomatosis, which is the term used frequently in the European Union for multiple myeloma, and he raised the question as to whether this is a new syndrome or not. He published the paper in *Acta Medica Scandinavia*, a leading medical journal in EU and in the world.

He emphasized the presence of anemia and hyperviscosity as features of the disease. He pointed out the presence of a homogeneous gamma globulin with electrophoresis. This gamma globulin component, known as IgM, was a large molecule. In fact, its molecular weight was 1 million, which is a very large protein indeed -- about 6 times larger than IgG, which is the most common immunoglobulin or protein we have in our blood. Dr. Waldenstrom called this a "giant" molecule.

WM affects just 3.6 persons per million among white men, and only 1.7 per million among white women. If you live in a city of 100 thousand persons, there would only be 1 case recognized every other year. You are indeed rare people.

The prevalence of WM is not higher in the African-American population, although the prevalence of multiple myeloma is twice as high among African-Americans as it is in the Caucasian population.

### **Symptoms**

Symptoms of WM include weakness and fatigue, which is mainly from the anemia that accompanies the disease. Some patients may first notice bleeding from their nose or their gums, and this is due to the hyperviscosity. Other patients may complain of blurring of their vision while they're watching television.

Other patients may present with recurrent bacterial infections because patients with WM are more susceptible to infection than a healthy person. However, there are many patients with WM who go along for years and years and have no infections, so you might not have any.

Some patients experience paresthesias, numbness and tingling usually of the feet and sometimes of the hands. Physicians call this peripheral neuropathy. As this progresses it can also involve the motor nerves, so you can also develop weakness of the extremities as well.

### **Physical Findings**

On physical examination, the patient is frequently pale due to anemia. In about 25% of patients the liver will be enlarged; however the liver function is usually very good, and you will not develop cirrhosis or any other serious liver disease. The spleen, which is on the left side, right under the rib cage, may be quite large.



*Robert A. Kyle, M.D., cont. on page 3*

*Robert A. Kyle, M.D., cont. from page 2*

Lymphadenopathy is enlargement of the lymph glands, usually in the neck but also under the arms and in the groin. This occurs in about one quarter of patients and in some cases it can be quite large.

Another physical finding may be retinal hemorrhages, and this is what causes blurring of vision. Your ophthalmologist may see hemorrhage in the back of the eye as well as dilatation of the veins.

### **Laboratory Findings**

A frequent laboratory finding is low hemoglobin. The exact level may be misleading because patients with WM have an increased plasma volume due to the large number of IgM molecules floating around in you're the blood. These draw in more fluid, increasing the blood volume, but your red cell count does not increase correspondingly. Therefore when you measure hemoglobin and hematocrit (which are measured as a percentage of your total blood), the numbers may be somewhat lowered due to dilution.

#### *Other Laboratory Findings*

The "sedimentation rate" may be high. Your physician should do a serum protein electrophoresis test if the sedimentation rate is elevated.

The leukocyte or white count is usually normal but may be low.

The differential count may show an increase in lymphocytes.

Platelets (necessary for blood clotting) may be low. If it is really low, you're going to have black and blue spots on your skin and you may have bleeding from your nose, gums, or GI tract.

Your blood cholesterol is usually low. Nobody knows why.

The creatinine level -- a measure of your kidney function -- is usually normal in WM, in contrast to multiple myeloma, where kidney insufficiency is common.

There is a distinctive electrophoretic pattern in the blood of WM patients. In the laboratory test, a small drop of your blood is placed on a gel and then an electrical current is applied. The proteins of your blood are separated on the basis of their size and charge. When one measures the protein bands in an electrophoretic strip, with an instrument called a densitometer, there is typically a tall spike in the gamma area in someone with WM whereas a normal person would have a broad hump. These numbers are reported in grams/deciliter. Usually in WM the size of this spike is 3g/dL or greater (or 30g/L).

When a spike is found in the electrophoretic pattern, we do not know what it is until we do a test called immunofixation.

The immunofixation serves two purposes: 1) it tells us that you have a monoclonal protein, that is one heavy chain, one light chain, and 2) it also tells you what that protein consists of.

There is another way to measure the IgM in your blood, and that is by a test called nephelometry. That is an accurate test but it measures both the monoclonal IgM as well as the polyclonal IgM. Don't have a nephelometry test at one clinic visit and switch at the next because this will lead to confusion.

Very frequently the IgG and IgA immunoglobulins, which are the other two main types of proteins in your blood, are decreased in WM. This is one of the reasons why you may be more susceptible to infections.

It's important to note that an elevated IgM level alone is not an indication for treatment.

#### *Urine Protein*

Your urine should be checked as well because about 80% of you will have three light chains in your urine. However the amount of light chains in your urine is generally very small and is of no real consequence under those circumstances.

#### *Bone Marrow*

I want to emphasize that very often when the bone marrow is aspirated and looked at under the microscope there may be very few cells - we call that hypocellular. But, you should also have a needle biopsy of your bone marrow, and when one looks at that, one finds a hypercellular bone marrow -- your bone marrow is full of cells and these cells are typically lymphocytes and plasma cells. There is an increase in mast cells in the bone marrow and that helps in making the diagnosis. In contrast to patients with multiple myeloma, bone lesions are very uncommon in WM.

Rarely, can one have an infiltration of the lungs by lymphocytes and plasma cells and sometimes this is manifested by pleural effusion, that is, fluid in the lungs, that may have to be tapped. Kidney function is usually normal. Bowel function is usually normal -- once in a while a patient will complain of diarrhea. Neurologically, neuropathy, that numbness and tingling of the hands and feet, is not uncommon.

### **Consensus Panel**

The consensus panel has agreed that to make a diagnosis of WM, one needs to have a monoclonal IgM protein but no particular size is needed. The bone marrow is infiltrated with plasma cells and lymphocytes. If the pathologist looks carefully, he will find that these plasma cells and lymphocytes contain IgM protein, they will have markers on them expressing CD19 and CD20 (and, less commonly, CD5).

*Research Posters, M.D., cont. on page 4*

## Differential Diagnosis

The differential diagnosis of a monoclonal protein in the blood, an IgM protein, may be a monoclonal gammopathy of undetermined significance (MGUS) and those patients have an M-spike in the serum that is <3g/dL and most importantly those patients have no symptoms or physical findings.

Multiple myeloma must be considered but here, in MM, 80% of the patients will have lytic lesions or abnormal bone x-rays, they will have more plasma cells in the bone marrow, a fifth of them will have kidney failure. The differential is not as difficult as it was years ago. In fact, prior to Dr. Waldenstrom's time, many WM patients were just lumped with those with MM.

Chronic lymphocytic leukemia also needs to be differentiated if you have an increased white count and an increased in lymphocytes.

Lymphoma, non-Hodgkin's lymphoma, the most common type of lymphoma, may be associated with a monoclonal IgM protein in the serum. So, your physician needs to differentiate WM from a patient with a non-Hodgkin's lymphoma with an accompanying monoclonal spike.

## Initiation of Therapy

When one is considering therapy, one does a complete history and physical examination and then one must make a diagnosis in the laboratory of WM. Before the patient is treated, the patient must have weakness, fatigue, fever, night sweats, weight loss – constitutional symptoms. Or you need to have a large liver or spleen (symptomatic hepatosplenomegaly) or bulky, very large lymph nodes (bulky lymphadenopathy). Or the development of anemia (Hb < 10g/dL) or low platelets (<100 x10<sup>9</sup>/L) Or hyperviscosity, symptomatic peripheral neuropathy, amyloidosis (precipitation of protein in various organs), symptomatic cryoglobulinemia, or cold agglutinin disease. Hyperviscosity may result in oral or nasal bleeding, blurred vision, headache; vertigo, ataxia, altered consciousness, fundoscopic findings (hemorrhages and dilated veins at the back of the eye).

Serum viscosity can be measured by a number of instruments in the laboratory. A normal value is < 1.8cP and it's very rare to have symptoms unless you have more than 4cP. The symptoms of hyperviscosity do not relate very well to your viscosity – you can have a high viscosity without many of the symptoms. You need to have the symptoms to make a diagnosis of hyperviscosity syndrome. Serum viscosity level is of limited value and it correlates poorly with symptoms.

## Follow-up

When you have smoldering or asymptomatic macroglobulinemia, you should be observed and not treated. Your physician needs to follow you, repeat your history/

physical examination and measure hemoglobin and M-Spike as appropriate. The frequency of measurement is variable and depends upon the size of the M protein and can be done anywhere between 3 months and 1 year.

## Questions

Does WM run in families?

There is a familial tendency for WM. It's uncommon to have your father with WM and you with WM. When I'm asked if a WM patient's family is going to have WM, I answer no and most of the time, I'm correct. It does have an increased tendency in families. But just because you have it doesn't mean your children will.

Do WM patients often have low cholesterol?

If you have low cholesterol, is this a true finding? When we repeat the cholesterol test, it's always low. But this may be a problem with the test due to the presence of the protein. A prospective study is required with two patient groups (WM vs non WM) to see if the frequency of heart disease is less in WM.

How do you differentiate multiple myeloma and cold agglutinin disease from a patient with WM?

Cold agglutinin syndrome – the patient has a very high titer of agglutination (1 to 20, 000; 1 to 40, 000) whereas in WM the results is 0 or negative.

MM patients typically have lytic bone lesions while WM patients do not. But occasionally 3 or 4% of WM patients can have lytic disease.

WM patients always have elevated IgM; with MM, you usually have IgG or IgA (20% of pts) or light chain only (up to 15% of pts). There is an occasional patient where it's a challenge to determine if her or she has WM or MM.

Does radiation damage bone marrow?

Yes, radiation damages bone marrow in the area that it was irradiated. There is no evidence that radiation therapy causes WM.

Are night sweats cause for concern?

Night sweats are non specific findings. We don't know much of the pathophysiology of night sweats. But normal people will have these if they bundle up and sleep. Hot flashes are frequently associated with night sweats. Night sweats are pretty nonspecific and you wouldn't want to demand therapy based on night sweats.

## Barbara L. Francis, M.A.

Navitas Cancer Rehabilitation Centers, Inc.

### *Integrative Supportive Therapies*



Cancer treatment should aim at retrieving for the patient a normal quality of life, both physical and mental. This is seldom done in more than a cursory fashion. The diagnosis of cancer is made on the basis of symptoms, physical and mental, which represent a loss to the individual. There are also other losses, including the physical and mental, but also social and financial. And cancer treatment adds its own problems to the mix. The true aim of rehabilitation is the retrieval of “quality of life.”

WM causes several changes in one’s life. Most common is fatigue, which may be biological or may be mental. There are also weakness, pain in the extremities, blurred vision, lowered immunity, loss of appetite, insomnia and many more possible side effects. And it may combine those effects with those of whatever other malady you may have - heart condition, diabetes, etc. WM probably will negatively affect your normal daily routine. When you need treatment, there are more negative side-effects. And you may also be burdened with financial stress. What, for example, is your insurance like? Can you afford treatment when it’s recommended? All this needs to be addressed. Even after treatment, recovery is not a linear process. And the restorative therapy must be individually tailored to your symptoms at each stage.

The patient needs total supportive care. Even after treatment is over, you need restorative therapy. You need to develop (or redevelop) the skills needed to get back to normal. We don’t want you in therapy for the rest of your life. We feel at Navitas that the professional has to assess the entire individual, physical and mental. We not only have our own medical director, we go back to your physician. We check your total physical condition before determining therapy. We look at your psychological situation and your nutrition. We try to assess your total situation, not only health, but interests, job, etc. It is also necessary to evaluate and assist the caregivers. Are they up to the job? Do they know what lies ahead of them? What assistance will they need, physical, mental, or financial? A plan of action is then drawn up and reviewed by the medical director.

One must be sure to explain to the patient why a particular course of care is desirable. Only thus can you be sure that the patient is on your side. We go through the question of insurance coverage to be sure the patient is clear on that. We try to relate everything, from psychological counseling to massage, to the patient from the beginning. We want at all

costs to reduce fear of the unknown. And we are constantly in touch with the patient’s doctors and their nurses.

Physical goals usually include the improvement of gait and balance and range of motion. Not only age, but medication can diminish physical ability. We do a lot of balance training to help avoid falls. Attention must be paid to the management of neuropathies, reduction of pain where present, and matters such as bone density (inactivity tends to weaken bones). And we must try to reduce depression and stress. Weight-bearing activity is helpful in all of this, and also improves the appetite. And it helps the patient to know that the therapist is really trying to help get him or her back to normal, not just going through the motions.

This type of program is helpful to the work of the oncologist. It helps decrease the side effects that interfere with treatment. Patient compliance with the physician’s orders is improved. The fact that there is increased surveillance, and that therapists confer on the patient’s situation with each other and with the oncologist means that many problems can be foreseen. We have actually discovered some early-stage cancers just from the side-effects the patient was exhibiting. And patient satisfaction with the total care program is improved.

To be most effective, cancer rehabilitation must be fully integrated. It must be individualized, allowing for the uniqueness of each patient. It must be continuous, following through from diagnosis to recovery. Its aim, above all, is to improve the patient’s quality of life. We feel we have made a positive difference to our patients. Resting heart rates have improved. There has been progress toward normal activity. Depression is reduced. What we can’t help are the patient’s finances and family/acquaintance support systems. But with our skilled staff, training by us and by knowledgeable patients, and the practice of integrated therapy from onset to recovery, we know we have made a positive difference in our clients’ lives, and led them toward more normal and happier existence.

## Irene Ghobrial, M.D.

Dana-Farber Cancer Institute

### *The PI3K Pathway*



Today I want to show you some of the Waldenstrom's research and clinical trials that we are conducting at Dana-Farber for all of you. I want to concentrate on what is called the PI3K pathway and give you some details about it.

Waldenstrom's macroglobulinemia is a name for a progression of diseases. It develops from MGUS (monoclonal gammopathy of undetermined significance, a name given by Dr. Kyle). MGUS may never develop into anything else. If it does, you pass through unsymptomatic WM to symptomatic WM. No treatment is needed until symptoms develop. And we now have treatments that do not damage stem cells.

Prognosis varies considerably. The older median disease-specific survival of 5 to 6 years has been supplanted in current literature by 11.2 years. But even this is from an old study. With newer drugs we may be able to turn WM into a chronic disease that you live with, not die from. All we can really say is that patients over 65, or who present with enlarged liver and spleen, or high beta-2 microglobulin levels seem to have poorer prognoses than the rest. And this is before the arrival of newer drugs. This we know will completely change.

One new prognostic factor we're looking at to differentiate between aggressive and indolent disease is the presence of free serum light chains. We have been using this in multiple myeloma and are now testing it in patients with WM. We are comparing these results with our usual markers of anemia, low platelets, high IgM and high beta-2 microglobulin. Perhaps it will be a better indicator of whether you will respond to treatment or not.

Standard treatments for WM vary from the older alkylating agents like chlorambucil through nucleoside analogs like fludarabine, rituximab, newer agents like thalidomide, bortezomib etc., through stem cell transplant. These need badly to be improved upon. The first two can damage stem cells. Not everyone responds to rituximab alone. Only about 10% of patients achieve complete remission, median time to progression is three years or less, and some agents do other mischief.

We need to find a better way. What is different about the WM cell? Why is it abnormal? Studies have shown that the activity of many proteins in the WM cell is elevated over the normal, e.g., HSP90. Getting rid of those proteins, e.g., using 17-AAG against HSP90, kills the malignant cell. We

are now trying to design experiments and clinical trials to help us understand why these rogue proteins cause the cell to become abnormal, how and why the disease acts as it does, and why some patients don't respond.

PI3 kinase is one of those proteins helping the WM cell survive and grow. What is known as the PI3K pathway can be targeted by drugs just as Velcade attacks another such pathway. The drug I am pursuing is called perifosene, and in the laboratory, where we are able to administer various concentrations to cells taken from patients, it kills off almost all WM cells. Normal cells are not adversely affected. Stem cells are not damaged. And it seems to work even in the presence of the types of cells, called stromal cells, that normally act to protect the WM cell; likewise in the presence of cytokines like IL-6. In mice, the drug controls tumors well.

After a year and a half of lab work, Phase II clinical trials have been set up. The dose of 150mg/day is administered by mouth, which simplifies treatment. Perifosene has shown no tendency toward inducing peripheral neuropathy, hair loss, low blood counts or other damage. The patient pool is from people who have been treated previously and have relapsed. Some of them are at this meeting. The main side-effect is nausea, quite controllable, and occasionally diarrhea. The trial is open at Dana-Farber and at a site in California, limited to previously-treated patients.

Velcade (bortezomib) is another drug active against WM. But Velcade is well known to cause peripheral neuropathy. So, in clinical trials on Velcade, we space out the Velcade and add rituximab to the mix. Those two-drug trials are ongoing, and may be opened to newly-diagnosed patients. This could be a very good drug for patients with high IgM.

Perifosene enhances the action of bortezomib, again with no effect on stem cells. And again adding rituximab increases the effectiveness. We are also trying other approaches and combinations with still other drugs, even including conventional drugs like fludarabine that can affect stem cells. The synergy is still obvious, with higher kill of the WM.

In these studies we are also trying to determine why some patients seem resistant to perifosene, using antibody microarrays among other things. Thus, in future, we may be able to predict whether a patient will respond or not, and avoid useless treatment. This resistance may involve something called PKC, which is strong in WM cells. In fact, you can kill the WM cell if you interfere with PKC, which we are able to do in animal experiments using a drug called enzastaurin. This is in clinical trials in other lymphomas; we are trying to get the producer interested in a WM trial, which is difficult considering the rareness of WM.

One of the questions researchers would like to solve is why WM cells concentrate or clump in the marrow. We can now

*Irene Ghobrial, M.D., cont. on page 7*

*Irene Ghobrial, M.D., cont. from page 6*

actually see the cells moving to and sticking in the marrow of mice. If we could prevent this “homing” we might find it easier to kill them, using existing drugs or many new ones we are beginning to work with. New drugs are being tried to force WM cells back into the bloodstream. Perifosene seems to have an effect here, preventing, even in very low doses, motion into and adhesion to the marrow, hopefully making the WM cells easier to kill. We can actually see, using modern machinery, individual WM cells in mice, the means by which they stick to the marrow, and the lack of this adhesion when we administer doses of what we call AMD3100, all without hurting the mice.

At Dana-Farber we have in 2006-2007 been running Phase II trials using perifosene alone, with rituximab, and with Velcade. We look for even more progress in 2007-2008, testing newer drugs like enzastaurin and AMD3100, alone and together with perifosene, rituximab and bortezomib. And we thank you for your support and your participation in these clinical trials.

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## **Stephen M. Ansell, M.D., Ph.D.**

Mayo Clinic

*Factors Regulating Immunoglobulin-producing  
B Cells in WM*



Waldenstrom's macroglobulinemia (WM) is a disease of B cells, the cells that produce immunoglobulins. We don't really know very much about Waldenstrom's. So unless we find out otherwise, we tend to carry over the assumptions we have gained from our study of the more common multiple myeloma (MM) or non-Hodgkins lymphoma (NHL). Not much has been studied

about WM as such. NHL is primarily a disease of immature B lymphocytes while myeloma is a disease of mature plasma cells. WM lies in between. I want to thank you for funding WM research, because WM's rarity makes it difficult to get money from the usual sources of cancer research funding.

B cells are an essential part of the immune system. We need to continually make them so that they can make antibodies to fight diseases. Waldenstrom's is a disease of B cells that are out of control, producing antibodies useless in fighting infection; the cells and antibodies are precise copies of each other (monoclonal). B cells go through various stages until they become mature plasma cells, each producing an antibody to a specific disease. They can go bad at different stages in their development, producing different cancers such as chronic lymphocytic leukemia (CLL), non-Hodgkins

lymphoma (NHL), and multiple myeloma (MM). WM comes at the stage of transformation from lymphocytes to mature plasma cells. The WM cells don't reproduce particularly fast; they just don't die, and so they and the useless IgM they produce continue to accumulate. Sometimes they produce little IgM, while in other patients they produce a great deal. We'd like to know why, so that we could control the disease.

The funding we have received has been used to try to understand a compound called B Lymphocyte Stimulator (BLyS). BLyS is a substance produced by many types of cells - monocytes, neutrophils, etc. It is essential to proper immune function, stimulating B cells to react against invaders. In this way, it is similar to another protein called APRIL. But it must be in balance: too much BLyS tends to promote lymphomas; too little and B cells do not properly mature. Experiments forcing mice to produce too much BLyS have led to lymphomas in those mice. Impeding its creation has led to poor B cell development and almost no immunoglobulins.

BLyS and APRIL attach to the cell membrane, binding to three receptors, called BAFF-R, BCMA (on plasma cells only) and TACI, which comes in several variations. They can stick strongly or weakly, giving the cell different signals, to grow and produce IgM or not. Malignant cells can make BLyS and APRIL themselves, increasing the concentration and compounding the imbalance. Thus, we find increased levels of these two proteins in WM patients' bone marrow.

What does BLyS do? We can show by experiment that it makes the B cell both survive longer and grow faster. It increases each B cell's production of IgM, especially in the presence of IL-6. And when WM cells are present, production of IL-6 increases greatly, feeding back information to the stromal (supporting) cells in the microenvironment, which become hijacked, stimulating greater production of these proteins. It becomes a vicious circle.

How can we block (but not totally) BLyS production and activity? That's the aim of this research. If we could reduce the concentration, perhaps the malignant cells wouldn't live so long. Because it's also connected with rheumatoid arthritis, four companies have answers to that question. The most interesting solution is to create decoy receptors that attach to the BLyS molecule and divert it without stimulating the cell. IgM levels are decreased. TACI-Ig, as it's called, works later in the B cell's development than, say, rituximab.

Rituximab treatment alone tends to increase the serum BLyS, showing the body is trying to increase its B cells, which may be counterproductive. And it doesn't work well in patients with plasma cell problems, because these cells don't usually show CD20. Perhaps the two treatments might work together. And maybe we can attack the cellular environment,

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particularly the mast cells that support the WM B cell. A compound called CDDO, for example, inhibits WM cells in preference to normal B cells, and also attacks the mast cells they need for support.

In brief, BLyS promotes B cells and collaborates with IL-6 to increase production of IgM. BLyS and IL-6 are produced by stromal cells in the marrow, including mast cells. New approaches may be profitable, including attacking both WM cells and stromal cells together.

### Answers to Questions:

1 – No single magic bullet against WM is on the horizon. We should probably use a “cluster bomb” approach, attacking IL-6, BLyS and other factors that promote the growth of WM.

2 – Long term effects of using things like TACI-Ig may include damage to normal cells, but so far there is little evidence of that. The body has an amazing capacity to suddenly create a quantity of new B cells to combat new infections, so there is little danger in the fact that we are depleting some, whether by this, rituximab or whatever.

3 – The fact that different individuals with similar marrow involvement show markedly different IgM levels may mean they are differently affected by BLyS.

4 – “Bad” B cells are those which have escaped from the normal tight regulation the body imposes. WM clonal cells are in that category.

5 – Maintenance rituximab might be more or less desirable on the basis of differences in individuals’ production of BLyS and other compounds. Clinical trials have not provided that data.

6 – Low levels of IgA and IgG in WM patients are due to a dearth of mature plasma cells, at least in part due to the fact that immature cells are taking up too much space and creating a poisonous environment in the marrow. We don’t understand the details.

## Rafat Abonour, M.D.

Indiana University

### Waldenstrom’s Complications



Waldenstrom’s is a disease involving an excess of plasmalymphocytes. The direct complications coming from Waldenstrom’s result from the infiltration of these plasmalymphocytes into the bone marrow and the lymph nodes. Complications may arise directly from this accumulation, or indirectly from the increase of their product, IgM. In the marrow, normal

processes of blood creation are crowded out, fewer red cells are created, and the result is anemia. Accumulation of cells in the lymph nodes causes these to expand and interfere with the operation of other bodily organs. They may cause the liver and spleen to enlarge. Indirect complications related to the increase of IgM in the bloodstream are numerous. Either the sick cells or this IgM may also be deposited in other tissues. Problems may also result not from the disease itself, but as side-effects of treatment.

The most likely problem to develop, particularly with an IgM of over 5000, is hyperviscosity of the blood, especially if it reaches 4 or 5 times the viscosity of water. But there is much variation from patient to patient in the threshold of danger, some patients showing symptoms with a viscosity as low as 3. Anywhere from 10% to 30% of patients are affected. Hyperviscosity can produce fatigue, bleeding, retinal damage, miscellaneous neurological effects (most notably peripheral neuropathy), vascular problems and more.

If cryoglobulins precipitate in low temperature situations (something like 10% of patients have this problem, usually involving Type I cryoglobulinemia), interference with blood flow may occur by simple blockage of blood vessels in the exposed extremities. Patients may have painful hands and feet, or Raynaud’s phenomenon may occur. Rarely, the kidneys also may suffer. Similar damage can result from cold agglutinin disease, where a reaction between IgM and red blood cells can produce a cryo-like situation, or even destroy red cells. This may occur in up to 10% of patients.

IgM may also be deposited in tissue and react to it. This may result in neuropathy, amyloidosis, renal problems and more. Neurologic damage usually shows itself in disruption of the peripheral nerves, the IgM reacting with nerve antigens. The result is a destruction of the myelin sheath that surrounds and insulates the nerve fiber, creating a situation much like the destruction of insulation in electrical circuits. Depending

upon what nerve is affected, there can be pain, numbness, or difficulty in balance or walking. Sensory nerves react with aching, discomfort or sharp pain. Motor nerve attack can cause difficulties in controlling motion. This may also be associated with cryoglobulinemia.

Amyloidosis occurs in about two percent of patients. It is the deposit of light chains in various organs, and the damage depends upon which organ is involved. In the nerves, it creates neuropathy. In the skin, it produces hive-like areas. In the intestines, there can be malabsorption of food, chronic diarrhea etc. It may also affect postural blood pressure regulation (e.g., dizziness on standing), impotence, bladder control, etc. Deposition of this sticky protein may affect heart, lungs, kidneys (high protein in the urine), and more.

Many of these problems are directly related to hyperviscosity. Since 80% of the IgM is in the bloodstream, plasmapheresis can be of help. Sometimes nothing else is required for years. This is particularly useful in the removal of cryoglobulins. But this is a superficial treatment, and it is probably best to treat the underlying disease.

Anemia can have several causes. Most obvious is blood loss, often in the digestive tract. But it can also be caused by red blood cells with a short life span. It may result from lack of iron or vitamin B-12, or their poor utilization. Or it can result from the crowding out of precursor cells, in WM this being due to the accumulation of lymphoplasmacytes in the marrow. Procrit, despite its current bad publicity, can often help.

The best approach to the relief of neuropathy is the reduction of the amount of IgM that is available to attack the nerves. This can be done by plasmapheresis or by using chemotherapy to reduce IgM production. The damaged nerves repair themselves slowly, but there are drugs to reduce the symptoms, of which the most popular is Neurontin.

Fatigue tends to be underreported and overlooked. After all, it's a subjective measure. To be noticed and treated, it must be serious enough to interfere with normal function. But that inability to function is extremely important, causing the disruption of normal life. Its causes are many, not limited to overexertion: anemia (of whatever cause), loss of muscle mass, poor metabolism, chronic stress, inflammation, poor nutrition, poor sleep patterns, nervous system toxicity (such as may result from thalidomide), etc. To treat it, we have to look for the cause, whether it be anemia, sleeplessness, pain, nutrition, inadequate activity level or some other illness besides WM. Then we have to try to correct for that. If there are other medical or emotional problems, treat them. Exercise, in particular, is very important to prevent muscular wasting. And that can mean as little as a half-hour walk three times a week.

In conclusion, to treat the complications of WM, first look for underlying causes. Be sure you are living a healthy lifestyle and get enough exercise.

### Answers to questions:

- 1 – The frequency of plasmapheresis depends upon the efficiency of exchange in local situations. Usually you are talking three to four liters, two or three times a week for two or three weeks, followed by maintenance.
- 2 – Plasmapheresis can be done by directly tapping veins, but a catheter is better and quicker.
- 3 – The choice of the best anemia treatment depends upon testing. Is the patient making too few red cells, or are they dying too quickly? Is there bleeding? Anemia can have several causes, so we have to check many factors, including reticulocyte count, etc.
- 4 – Aspirin cannot reduce serum viscosity, but may be useful for other reasons if used carefully on your physician's advice.
- 5 – Loss of muscle mass can be age-related as well as cancer-related. We can't always tell the cause. It is important to keep up the activity level.
- 6 – Depression can be a part of fatigue.
- 7 – So-called blood thinners, like aspirin, are not usable to reduce viscosity, only to reduce coagulation.

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## Constantine S. Mitsiades, M.D., Ph.D.

Dana Farber Cancer Institute

*Tailoring Therapy to Molecular Profiles –  
New Directions for WM Treatment*



Dr. Mitsiades presented results of pre-clinical studies partially funded by the IWMP on four new classes of therapeutic agents for WM: proteasome inhibitors like Velcade (Bortezomib); immunomodulatory thalidomide derivatives (IMiDs) such as Revlimid (Lenalidomide) and Pamidomide (Actimid); inhibitors of hsp90 (heat shock protein); and histone deacetylase inhibitors. Two of these new classes of drugs have already been studied in clinical trials in WM and are, in effect, now being used to treat WM.

The best known of these new agents is Velcade. Velcade targets the proteasome, an intracellular structure that essentially works as a garbage disposal system for unused

*Constantine S. Mitsiades, M.D., Ph.D., cont. on page 10*

proteins in all cells. Tumor cells, especially those similar to WM, seem to be very sensitive to any disruption of this garbage disposal system, perhaps due to the overproduction of proteins such as IgM by WM cells and IgG by multiple myeloma (MM cells). There appears to be also a very complex relationship between the proteasome and the molecular messenger molecule I B/NF- B pathway. This pathway is involved in the regulation of growth of the tumor cells and resistance to chemotherapy. Therefore, Velcade appears to kill WM cells through at least two mechanisms, and this has been demonstrated in laboratory and eventually in clinical studies.

The immunomodulatory thalidomide derivatives (IMiDs) have been actively studied since 2001 in MM cells in particular. Based on these studies, four mechanisms of tumor cell kill by this class of drugs have been described: IMiDs starve the tumor cells from the blood supply that feeds them (anti-angiogenic effect); IMiDs enhance the tumor killing properties of T-lymphocytes and natural killer cells; IMiDs block some of the interactions between tumor cells and other (stromal) cells in the bone-marrow micro-environment; and finally IMiDs seem to directly kill tumor cells by a mechanism not yet fully understood. Laboratory and clinical studies have confirmed that IMiDs drugs are active in WM cells, some more than others.

Heat shock protein (hsp90) is an interesting protein used by normal cells and tumor cells to regulate the shape (the correct folding sequence and thus the specific functions) of proteins that cells use to stimulate their multiplication and survival, particularly in the context of treatment with chemotherapeutic agents. The hsp90 molecule is involved in multiple critical pathways in the cell, including the now familiar Akt pathway (target of the drug Perifosine). Laboratory in vitro studies of the hsp90 inhibitor molecule have demonstrated activity against WM cells in doses that are non-lethal and that result in what is believed to be manageable side-effects. Clinical studies are underway in some cancers other than WM at present.

The last class of new agents is perhaps the most intriguing of all. Histone deacetylase (HDAC) is an important protein complex that regulates how tightly bound (or put in “storage”) the DNA is to structures called nucleosomes. HDAC inhibitors causes the “unwinding” of DNA, and by mechanisms that are not fully understood, renders some important tumor-related genes on the DNA to be either more active or more commonly less active (down-regulated). In the case of tumor cells like MM and WM, HDAC inhibitors, like the drug SAHA, make the tumor cells less able to proliferate, rendering them more differentiated (less immature), and more prone even to spontaneous cell death. Laboratory evaluations of SAHA in WM have demonstrated WM cell death with what is believed to be manageable side-effects;

in fact, the FDA has approved SAHA for the treatment of a rare cancer, cutaneous T-cell lymphoma.

Dr. Mitsiades began the second half of his presentation by reminding us all that it may be unrealistic to believe that using one drug by itself will be sufficient to effectively control, or cure, WM. Combinations of drugs most assuredly will result in better outcomes. But what drugs do we use, and in which patients? Thanks to IWMF-funded research, Dr. Mitsiades and his team of researchers have undertaken molecular profiling studies to predict the clinical response of WM cells to certain agents, most commonly Velcade. In an elegant study, the combination of Velcade and hsp90 resulted in encouraging results. Molecular profiling studies, also known as gene expression profiling, has shown that certain genes are either up-regulated or down-regulated following chemotherapy. More important than identifying the individual genes however is the identification of patterns of gene expression following a specific treatment protocol. There are some formidable challenges to this approach: current technological limitations, difficulty in analysis of data and pattern recognition, and the requirement for relatively large numbers of samples to satisfy statistical validity. Nonetheless, Dr. Mitsiades is confident that through continued support for research in pharmacogenomics, genetic markers will be developed that will enable clinicians to predict resistance of WM cells to chemotherapeutic agents and thus truly permit “individualized” therapy in WM using less toxic and more efficacious combination therapies of newer drugs.

Dr. Mitsiades thanked the IWMF for its continued financial support, and noted the continued inspiration that he and numerous WM researchers derived from WM patients.

### Answers to Questions:

1 – Molecular profiling studies are being used in other cancers, specifically in lung cancer for example, but the studies are by nature quite difficult, require large samples, and are often like “looking for a few needles in a haystack”.

2 – Genetic profiling studies can vary in cells following treatment, and living cells that have been treated, but have not yet perished, are used. Comparison of non-treated cells, recently treated cells, and cells in various stages of cell death are needed.

3 – Tumor cells rely on heat shock protein (hsp90) to survive much more than normal cells.

## Gwen L. Nichols, M.D.

Hoffman-La Roche Pharmaceuticals

### *Conventional Treatment Options*



We are all interested in new developments from the laboratories and clinics. The future looks bright. But what can we do *today* to treat WM patients?

What is WM anyway? We don't really know, which complicates the issue. What makes a WM cell different? Even the doctors aren't sure, though we are trying to find out.

We define the disease first and foremost as an IgM monoclonal gammopathy. There is an excess of immunoglobulin M, all of whose molecules are identical. The quantity can vary; we no longer insist that it be high. And in the bone marrow we find a lymphoplasmacytic lymphoma, mature B cells that somehow can't change into plasma cells as they should, lining up along the bone. All these cells are identical, of the same immunophenotype; they have the same surface markers, differing from the normal; they are clones. And those markers tell us that the cells are not chronic lymphocytic leukemia (CLL), mantle cell lymphoma, or other B cell cancers. WM is a B cell malignancy like NHL [non-Hodgkin lymphoma], has surface markers much like those of CLL, and processes immunoglobulins like multiple myeloma. But it occurs at a unique stage in B cell development, and requires different treatment from those other diseases.

WM does not include all cases where too much identical IgM is found. Many other disorders can produce the same effect, often with no damage being done. More people with excess IgM have other cancers than those who have WM. Or there may be no cancer at all. About half the cases we simply have to classify as MGUS, monoclonal gammopathy of undetermined significance.

Even if you have WM, do you need to be treated at all? In many cases, there are no symptoms, and no real reason to treat. Lymphoid cancers are not like a solid-tumor cancer, where quick removal is mandatory. Despite popular belief, quick action may gain you nothing. But in other cases the excess IgM or the accumulation of cells in the bone marrow can cause problems. Everyone is different. How inconvenient are your symptoms? How uncomfortable and how dangerous are the available treatments? It's a balancing act. So what I'll try to do is show some of the choices.

Sometimes the IgM attacks the myelin sheath that insulates nerve fibers. The bare nerve is exposed and is very sensitive, resulting in peripheral neuropathy. Sometimes the presence of many WM cells in the bone marrow makes it difficult for

that marrow to produce red cells, and the result is anemia, or they overflow into your spleen and lymph nodes, causing them to enlarge. Less frequently the IgM is deposited within organ tissue (amyloidosis) or settles out of solution in cold conditions, blocking blood flow (cryoglobulinemia). And quite often the heavy IgM molecules cause the blood to become thicker (hyperviscosity), which can rupture capillaries in the eyes, brain or elsewhere.

Assuming treatment is needed, what do we now have in our arsenal that we know works against WM? Our choice may depend on the particular symptoms you are experiencing. We have plasmapheresis (physical removal of IgM from the blood), alkylating agents, nucleoside analogs, monoclonal antibodies, and combinations of these. How do we decide which to use in a given case? We look at the patient's symptoms, and we consider possible side effects. Sometimes we make the right choices from our arsenal, sometimes we don't.

Plasmapheresis is a quick and sure method of reducing high IgM levels in the patient's blood. It's useful in reducing high blood viscosity, and also helps if the IgM is chemically attacking your nerves or other systems, or precipitating out in cryoglobulinemia. Or it can be used to clear out IgM before rituximab therapy. The problem is that it is temporary. We haven't dealt with the underlying disease that caused the high IgM in the first place. Within a short time the IgM level has risen again and we have to do the job over.

Alkylators give about a 50% response rate, with few complications, and have been effective against B cell malignancy for many years. They work by damaging DNA. Chlorambucil is the most commonly used. Their effectiveness can be aided by steroids, and they have over time given a survival of 5.4 years. They are cheap, and they have the advantage of being taken by mouth. But long-term use may lead to leukemia. Combinations of alkylators may improve the outcome somewhat. Considering that the ill effects usually do not appear for 5-20 years, this may be a reasonable compromise, or it may not be. Cost may also be a factor. Chlorambucil treatment costs only a few dollars, compared to thousands for most other choices

The rest of our options involve intravenous chemotherapy, something of an inconvenience. Nucleoside analogs are also DNA damagers, frequently used if the patient has large lymph nodes or low blood counts. The chief of these are fludarabine and 2CdA. They give a fairly long response time, often several years. They are useful if there is spleen or lymph-node involvement, or low blood counts. They work faster than the oral alkylators, which may be a factor. Response rates are roughly equivalent to alkylators, though you have to be careful in deciding what a given experimenter

*Gwen L. Nichols, M.D., cont. on page 12*

means by response. One positive reason for using them is that the duration of response is fairly long.

Monoclonal antibodies, chiefly rituximab, more directly attack the diseased cells, but with only a 30-40% response rate when used as first therapy, and apparently do not work for every patient. They may not be very good if there are large lymph nodes that need to be reduced, or if the patient has significant liver or spleen enlargement. And the response is delayed, sometimes several months, so if you can't wait that long, this is not the way to go. There are concerns that many patients develop an IgM flare, where the immediate response is rapid increase in the IgM level, which if the initial level is high anyway can result in eye damage and other problems. Be sure your doctor is aware of this danger, so that if you have a high or sticky IgM you can get plasmapheresis before rituximab, just to be safe. The duration of response from rituximab is only about a year, and the question of its use as a maintenance drug is still not determined.

A way of reducing the IgM flare is the use of combinations, rituximab plus a chemotherapy. One such combination is an old alkylating agent combination called CHOP, used together with rituximab. If you want, for example, to reduce the WM burden before transplant, it's a very good therapy. One must be monitored, though, because CHOP has cardiac implications, and blood counts will go haywire. Another is the use of rituximab along with fludarabine or 2CdA. In both cases the effects are synergistic and the IgM reduction is rapid. Why not, then, standardize on these? Because they can damage the bone marrow, particularly stem cells. While normally this would simply mean low blood counts, it could result in leukemia and be fatal, so we don't take it lightly. And having a malignancy implies that you already have some chromosomal damage. The risk could be as high as 8% over a 10-15 year period. Is it worth it in your case? It's something to talk over with your doctor.

So there are many possible treatments, from plasmapheresis through alkylators and nucleoside analogs to murine antibodies like rituximab or even marrow transplants, and also combinations of them, and more are in the offing. And there are many different presentations of WM. The goal, in consultation with your doctor, is to try to turn your WM into a chronic illness, not a terminal one. You can help in this by backing and participating in clinical trials, and by providing financial backing. Since WM is so rare, you can't count on any pharmaceutical company to spend billions on this disease. It's your interest that keeps the research going.

## Rafat Abonour, M.D.

Indiana University

*Transplant in Waldenstrom's macroglobulinemia*



The question of choosing a bone marrow transplant in WM is not one that is easily answered. Waldenstrom's is an indolent lymphoma. Not every patient needs treatment. It is not only rare, but it is

also not a one-size-fits-all disease. Transplants need to be considered as a custom-designed treatment, not something for everyone. No two patients require the same treatment, and consideration must be given to the individual's overall condition. Immediate treatment may in fact reduce survival. This means that a transplant should not be considered immediately. It is also not clear how best to measure the success of treatment: lower IgM levels, long-term reduction of symptoms, length of survival are all possible measures.

Of the standard single-drug treatment options available, chlorambucil yields a response in about 50% of patients, with a slow recurrence and maybe a 5.5-year median survival. Fludarabine gives a 36% response and 7 years. With 2CdA, we see 50% and 6 years. Rituximab works 50-60% of the time and gives a time-to-disease-progression of about 27 months; overall survival has not yet been determined. These are the references against which transplants need to be measured.

How should we measure success or failure of a transplant? What basis should we use to determine if a patient is a candidate for transplant? Should everyone have stem cells collected for a rainy day? These are not idle questions, nor is there one simple answer. The transplant process involves higher dosages of chemotherapy, which could backfire. First, one collects a "graft" of stem cells, either from the patient (for an autologous transplant) or from a matched donor (an allogeneic transplant). That done, heavy doses of chemotherapy are given to kill the patient's immune system, including the WM cells. Then we introduce the graft to start a new immune system. With an autologous transplant, things should go relatively smoothly from there; if the graft is allogeneic, there is the danger of warfare between the foreign immune system and the patient's body, so-called "graft-versus-host disease" (GVHD).

Peripheral blood stem cell collection, as now used, is better and easier than marrow collection. We now know how to mobilize stem cells to get them into the bloodstream. We

have better patient management with the use of growth factors, better ways to fend off infection, and better control of GVHD. Autologous transplant, with a death rate of about 5%, remains much safer than allogeneic, where the mortality rate can reach 40%.

The usual requirements for considering a transplant include: (i) age -- up to 70 for an autologous transplant (has been done successfully to 78 in multiple myeloma) and 50 for an allogeneic transplant, (ii) disease that is responsive to chemotherapy, (iii) adequate organ function, and (iv) freedom from other diseases. Complications can be regimen related (e.g. an adverse reaction to chemotherapy), graft related (e.g. a reaction to the volume of transplant or an allergy to the chemical used to prevent crystallization during the freezing cycle), and post-transplant related (e.g. infection, shingles, graft failure, adverse drug reactions, etc).

Donor transplants (allogeneic) are used primarily with the young. The big danger is graft-versus-host disease. We want graft-versus-cancer, but not graft-versus-everything. The use of a non-myeloablative transplant (where the host's immune system is suppressed but not killed by chemotherapy) has reduced this problem but not eliminated it. This type of mini-transplant can be used on older or less healthy patients. It can sometimes even be done on an outpatient basis. But one must watch carefully during the first 7-10 days after the procedure to avoid infection while the patient has essentially no immune system.

What about transplants in Waldenstrom's specifically? The data is limited; there have been few transplant patients. But transplants do work well in cases of related low grade lymphoma and in myeloma. Survival in these diseases is usually longer than can be attained through conventional chemotherapeutic regimens. Neither type of transplant totally cures; there is always relapse. There is also, of course, a problem in collecting enough viable stem cells for an autologous transplant if the patient has had heavy chemotherapy, especially fludarabine. And there is some mortality in the first 90 days after transplant, perhaps 5% in autologous and 40% in allogeneic.

Transplant in WM is perhaps best chosen for younger patients with poor prognosis. For best results, if autologous transplant is being considered, early collection of the necessary stem cells is advisable.

### Answers to questions:

- 1 – We have no samples of double transplants in WM.
- 2 – In preparation for transplant, CD20-positive cells should be attacked. A fully humanized antibody would be nice, but we don't yet have it. Rituxan is better than the other chemotherapeutic agents now available because it works

against resting cells, not just those in the process of division, and also because it doesn't affect stem cells..

3 – We like to collect stem cells when there is little residual disease, so some treatment before collection is probably useful.

4 – Purging the graft of WM cells is not very successful. The best purge is rituximab before collecting stem cells from the patient.

5 – Interferon may make mobilizing stem cells difficult, but it's not a permanent problem.

6 – Higher marrow involvement is no longer a problem to collection. We can now go with 50% instead of the former 25%.

7 – Frozen stem cells can last for years in storage if properly maintained.

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## Steve P. Treon, M.D., Ph.D.

Dana Farber Cancer Institute

*Genetic Basis, Pathogenesis and Therapy of Waldenström's Macroglobulinemia*



Dr. Treon has been working on WM since 1999. He was first introduced to this disease when asked to speak to a New England WM Support Group on behalf of Dr. Ken Anderson.

Dr. Treon begins his talk by recognizing the understated genius of Dr. Jan Waldenström, the unassuming Swedish physician

who first described WM almost half a century ago, and then noting the Athens 2002 Consensus Panel Recommendations on the clinicopathological definition of WM: the presence of a serum monoclonal IgM protein, irrespective of serum level and an underlying pathological diagnosis of lymphoplasmacytic lymphoma using REAL/WHO criteria.

“Why do I have WM?” is perhaps the most common question a newly diagnosed WM patient poses to his physician. To date, a number of predisposing and inciting factors have been identified: chronic antigen stimulation (drugs – malarial type drugs in particular, infections, agent orange); familial predisposition in 20% of cases; an Ashkenazi (Eastern European) Jewish background in 19.8% of cases; and most importantly from a pathogenesis standpoint the additional diagnosis of 20-25% of WM patients who concurrently have common variable immunodeficiency syndrome (CVID).

A familial predisposition is noted in 20% of WM patients. These patients have a first degree relative with any B-cell malignancy, present with WM at a younger age, typically have greater bone marrow involvement, and have a higher serum IgM level at diagnosis. Recent genetic studies supported by the IWMF have actually uncovered previously undiagnosed WM in asymptomatic family members of WM patients!

Many WM patients have noted that despite successful therapy, their IgG and IgA levels never return to normal. This hypogammaglobulinemia, also noted in common variable immunodeficiency syndrome (CVID – which affects up to 20-25% of WM patients), is closely tied to the function of a membrane receptor TACI. The TACI receptor binds to the serum proteins BLyS and APRIL (see Dr. Steve Ansell's talk) and cause the lymphoplasmacytic cell in question to stop producing IgM and mature to the IgG and IgA producing plasma cell. Mutations in the TACI receptor gene eventually lead to defective cellular signals that prevent the change of IgM producing cells to IgG or IgA producing cells. Mutations in the TACI gene are commonly found in 20% of patients with CVID, and are also found in WM patients with hypogammaglobulinemia. The severity of the hypogammaglobulinemia is often directly related to the number of mutations in the TACI gene. Experimental mice that have no TACI genes (TACI knockout transgenic mice) are predisposed to lymphomas, and patients with CVID have up to a 300 fold increased risk of developing lymphomas. For many WM patients, mutations in the TACI gene may be the “backdrop” event that leads to the development of WM. Mutations in the genes for proteins that interact with TACI such as APRIL and TRAF-2 has also now been identified.

Why do WM cells prefer to home-in and live in the bone marrow predominantly whereas most other lymphomas prefer lymph nodes and the spleen? The answer may lie in the presence of mast cells (cells usually involved in the allergy response), increased in number, and noted to surround clusters of WM cells in the bone marrow. These mast cells “befriend” WM cells and promote the growth of WM cells (and normal B-cells in general) by releasing a very potent cytokine called CD-40 ligand (CD-40L). Blocking the CD-40L inhibits mast cell induced proliferation of WM cells.

Conversely, what signals do the WM cells send to the mast cells to encourage the release of CD-40L? A serum protein called soluble CD-27 (sCD-27) has been noted to be elevated in WM (and MGUS) and these serum levels of sCD-27 parallel perfectly the corresponding IgM numbers in the plasma. Levels of sCD-27 are a very accurate measure of WM tumor burden, not affected by the Rituxan “spike” or by plasmapheresis. WM cells make a very large amount of sCD-70, which in turn binds to the CD-70 receptor on mast cells, which in turn causes the release of CD-40L, the potent inducer of WM cell growth. Blocking the CD-70 receptor

by using a new monoclonal antibody (MAb - similar in concept to Rituxan) called SGN-70 has been demonstrated to successfully target WM cells in a new WM mouse model (WM SCID-hu mice) developed by Dr. Treon's lab. Additional targeting of the CD-52 receptor on mast cells by the MAb Campath, or of the CD-117 receptor on mast cell by the drug Gleevec has also been effective in blocking the interactions between mast cells and WM cells thus reducing WM tumor burden.

Dr. Treon did review the Consensus panel recommendations for therapy of Waldenström's macroglobulinemia established at the 3rd International Workshop on WM held in Paris in 2003. The IWMF has published a booklet on this important conference and the reader is referred to this booklet for further information. Dr. Treon did focus on the now well known Rituxan “spike” phenomenon, recommending judicious use of plasmapheresis in select patients. The use of WM therapy is now increasingly becoming more individualized, as certain therapies can impact patients adversely given their clinical specifics.

The results of clinical trials using immunomodulatory drugs such as Thalidomide and its derivative Revlimid in WM were presented. These drugs have been shown to boost the antibody-dependant cellular cytotoxicity (ADCC) effect of the immune system and Rituxan twofold with Thalidomide and threefold with Revlimid. More importantly, the addition of Thalidomide to Rituxan overcame the poor prognostic factors associated with singular WM treatment with Rituxan: elevated IgM, unfavorable polymorphism profile of the FC IIIA receptor, and elevated serum  $\kappa$ 2 microglobulin. Regrettably, the use of these drugs was not without side-effects. The effectiveness of Thalidomide is directly related to the dose used, and so are the neuropathy-like side-effects. Revlimid, despite drastic dose reductions, caused dangerous rapid reductions in WM patient's red blood cells, leading investigators to abandon the use of this drug in WM altogether.

Dr. Treon briefly touched on the issue of maintenance Rituxan (MR). There are no trials presently evaluating MR in WM, and the optimal scheduling and dosing of Rituxan remains to be determined. However, based on preliminary work done with MR in other indolent low-grade lymphomas, and based on his own observations, Dr. Treon does recommend MR.

Other investigational agents such as Velcade are currently being evaluated in WM. Velcade appears to be very active in relapsed/refractory WM, but the incidence of therapy related neuropathy remains unacceptably high. Velcade may also falsely lower IgM levels in some patients in relation to their actual bone marrow involvement. The use of sCD-27 serum levels noted earlier in this review may help resolve this issue. Most new trials of Velcade in WM now use reduced dosing/

scheduling of Velcade in order to reduce the incidence of neuropathy.

The phase II clinical trial using of the MAb Campath (alemtuzumab), which targets the CD-52 receptor on the mast cells and WM cells, was quite successful leading to an overall response rate (ORR) of 81%, and, for the first time ever in MAb therapy, a complete remission (CR) in one patient. A new and exciting clinical trial, the ART trial, will evaluate alemtuzumab (Campath), Rituxan and Thalidomide. We know that the more antibodies that coat a specific target (WM cell), the better the immune response. Addition of the immunomodulatory drug Thalidomide should also boost the effectiveness of these MABs.

Dr. Treon touched on the WM Viagra trial, a very popular and rapidly accrued clinical trial. Viagra does have an effect on WM cells, but after approximately six months of therapy, most WM patients had become resistant to Viagra and their IgM levels had began to climb once again (for more information on the specific actions of Viagra in WM please see the 2007 Ed Forum report on Dr. Mitsiades's talk).

Gleevec, the "miracle" drug in chronic myeloid leukemia (CML), targets the stem cell factor receptor present on the mast cells and on the WM cells. A clinical trial is now fully enrolled, and preliminary reports show promising responses.

Lastly, Dr. Treon discussed the serendipitous finding of the inverse relationship often seen between WM patient's cholesterol levels and their IgM levels. It appears that 42% of WM patients have abnormally low levels of serum total cholesterol (< 160 mg/dl). Certain types of cholesterol lowering drugs, called statins, have been shown to induce cell death (apoptosis) in WM cells at typical pharmacological doses used by many for cholesterol reducing therapy. Of the statin drugs Lipitor, Pravachol and Zocor noted in preliminary studies, Zocor (simvastatin) is the more active in WM. A clinical trial using this drug will soon be underway.



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