


**Update on Waldenström
Macroglobulinemia (WM)**



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Slide 1 - Update on Waldenström Macroglobulinemia (WM)

Lizette Figueroa-Rivera:

Greetings and welcome to The Leukemia & Lymphoma Society's Update on Waldenström macroglobulinemia Education Program. On behalf of the Leukemia & Lymphoma Society I would like to welcome you.

The Leukemia & Lymphoma Society exists to find cures and ensure access to treatment for blood cancer patients. Our vision is a world without blood cancer. For more than 60 years LLS has helped pioneer innovation such as targeted therapies and immuno therapies that have improved survival rates and quality of life for many blood cancer patients. We advocate for patients, survivors and their families helping them navigate their cancer treatments and ensuring that they have access to quality, affordable and coordinated care.

We are fortunate to have as our presenter Dr. Stephen Ansell, one of the nation's leading experts in Waldenström macroglobulinemia. We appreciate his dedication to supporting our mission and his commitment to caring for patients living with blood cancers. Dr. Ansell is Professor of Medicine Division of Hematology at the Mayo Clinic in Rochester, Minnesota. We thank Dr. Ansell for volunteering his time and sharing his knowledge with us today. Dr. Ansell, I'm now privileged to turn the program over to you.



Disclosures

Stephen M. Ansell, MD, PhD has nothing to disclose.

Slide 2 - Disclosures

Dr. Stephen Ansell:

Thank you very much. I have no disclosures.

Waldenström macroglobulinemia

Treatment approaches for newly diagnosed and
relapsed disease

Stephen Ansell, MD, PhD
Mayo Clinic

Slide 3 - Waldenström macroglobulinemia

So, thank you to everybody for joining us with this program and the focus as we are moving through the program is on Waldenström macroglobulinemia and specifically on treatment approaches for newly diagnosed and for relapsed patients.

Topics to be covered -

- What is Waldenström macroglobulinemia?
- Who needs treatment?
- Standard treatment options –
 - Newly diagnosed patients
 - Relapsed patients

Slide 4 - Topics to be covered

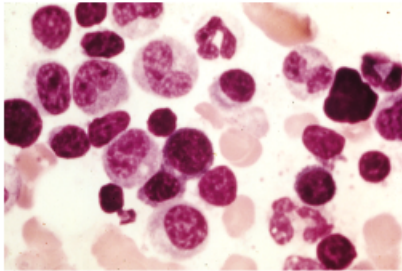
So, the goal today is to cover three topics the first of which is what exactly is Waldenström macroglobulinemia. The second is to talk about which patient when they present, needs treatment. The third is to talk about what are those standard treatments with a specific focus on newly diagnosed patients and then subsequently a further discussion about what to do if the disease comes back.

What is Waldenström macroglobulinemia?

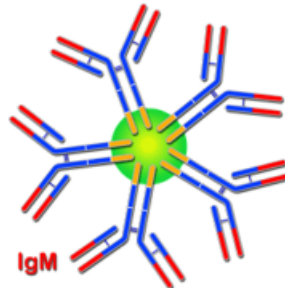
Slide 5 - What is Waldenström macroglobulinemia?

So, the first thing to discuss is exactly what is Waldenström macroglobulinemia and I think it's important for folks to understand that Waldenström macroglobulinemia is really a disease with two problems.

Waldenström macroglobulinemia “A disease with two problems”



Lymphoplasmacytic infiltrate



Monoclonal IgM protein

Gertz et al. The Oncologist 2000;5:63-67

Slide 6 - Waldenström macroglobulinemia: “A disease with two problems”

So, shown here in this figure on the left is what is called a lymphoplasmacytic infiltrate and what that means is there are cells present in your body called lymphocytes that when activated, turn slowly into plasma cells and these plasma cells make antibodies, and this is a natural reaction to exposure to viruses, bacteria, pollen or whatever.

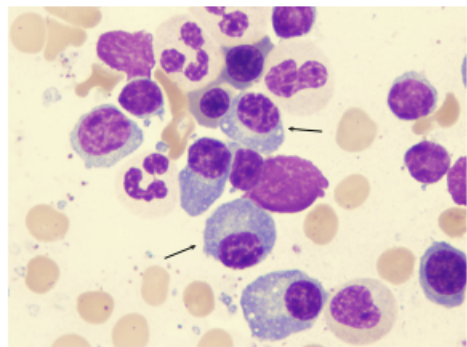
However, when those cells become genetically unstable and make a genetic mistake, the disease can actually develop into a cancer problem and so lymphoplasmacytic lymphoma is this infiltrate of cells that are present within the bone marrow, typically but also can be other places in one's body. It can be in lymph nodes, it can be in liver or spleen or other sites throughout the body but most commonly it's in the bone marrow as that's the place where these cells are born. And the reason it's a lymphoplasmacytic infiltrate is the cells are stuck in transition from the lymphocytes through to the plasma cells.

So, as you can see in the figure there are some cells that are small and there are some cells that are a lot bigger. The smaller cells are the lymphocytes, the bigger cells are the plasma cells or the ones that are becoming plasmacytoid and the reason this matters is that they are making an antibody and that's the second part of the problem.

So, shown on the right is the monoclonal IgM protein. So, again the first way in which your body reacts to pollen or infections or whatever is to make a large monoclonal antibody, large protein molecule that you can see here, an IgM molecule that will stick to whatever the threat to the body might be. When however, these cells become abnormal and when they become cancerous they now start to make a substantial amount of this protein and over time this protein begins to accumulate within the body.

The reason also that it's important to highlight in this figure is the fact that these are big molecules, meaning they are actually five different monoclonal antibodies all stuck together and these five monoclonal antibodies that you can see make up this IgM. This large molecule has a number of problems in that firstly, it's very sticky and secondly, it's very likely to be able to stick to critical organs and critical tissues causing substantial problems.

Waldenström macroglobulinemia Morphology and Immunophenotype



- Lymphoplasmacytic infiltrate (usually intertrabecular)
- Immunophenotype - surface IgM+, CD19+, CD20+, CD79a+ and PAX5+. CD5-, CD10-, CD23-.
- exclude CLL and mantle cell lymphoma
- MYD88 L265P is the most common genetic abnormality seen
- del(6)(q21) and CXCR4 mutations are also seen

Treon et al. N Engl J Med. 2012;367(9):826-33.
Hunter et al. Blood. 2014;123(11):1637-46.

Slide 7 - Waldenström macroglobulinemia Morphology and Immunophenotype

So, firstly just to highlight a little bit more in the way of detail related to this lymphoplasmacytic infiltrate. So, what you can see here again in the figure and you can see the arrows, are the cells with the blue parts sort of, they sort of have dark blue in the nucleus and much lighter blue that you can see around the outside. That lighter blue is all of the IgM that's being stored up in the cell before it's given off.

The second thing that's important is on the outside of these cells are a number of different proteins that can be identified and that's what doctors will use to make the diagnosis after they've done a bone marrow test. They will look to see whether these cells express proteins like the CD20 molecule, sometimes CD138 and a variety of other proteins all of which tell the pathologist that this is a lymphoplasmacytic process or a lymphoplasmacytic lymphoma.

The second thing that's really important for a pathologist is to be dead sure that this is not a different kind of lymphoma. So other kinds of lymphoma that are commonly excluded include things like chronic lymphocytic leukemia or mantle cell lymphoma or even diseases called marginal zone lymphoma. And one of the ways in which the pathologist can do that and we will circle back to more conversation a little later around some of the genetic tests, is to do a test for an adapter protein which is called MYD88 and MYD88 is the gene that codes for that protein. And as you can see there is the L265P mutation which means that there's actually a change in that gene and the way it's made up and when it does that it changes the structure of the protein just slightly, and that actually makes that protein hyper functional meaning it works more than it should.

That's very commonly seen in patients with Waldenström macroglobulinemia. In fact, depending on which study you look at it's sometimes 90% maybe even higher, maybe 95% of patients with Waldenström macroglobulinemia will have this MYD88 mutation. Other mutations and again we'll talk a little more about this as we go through this presentation can be in a different gene called CXCR4. As I mentioned earlier on the outside of these cells are various proteins, some of these are to allow the cell to know where to go and typically as I mentioned, this is a disease that's in the bone marrow.

CXCR4 is the way in which the cell works out where it needs to be. It's part of the homing device or the tracking ability for these cells. Mutations that happen in that little, almost antenna if you like that's on the outside of these

cell can make cells more resistant to chemotherapy or to some of the new drugs that we'll talk about later in the program.

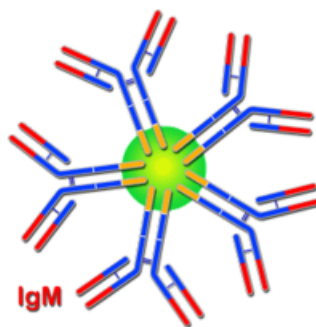
So, what I'm hoping folks listening to the program will understand is that a lymphoplasmacytic infiltrate of this lymphoplasmacytic lymphoma is commonly detected in the bone marrow, can also be in other sites like in lymph nodes or spleen and your doctor will typically do a bone marrow test and often a CAT scan or PET scan to look for all of these sites of disease to detect the length of lymphoplasmacytic infiltrate and the pathologist will help to make sure the diagnosis is correct.

Waldenström macroglobulinemia

Monoclonal IgM

- Symptoms related to the monoclonal IgM protein are attributable to -

- its characteristics in the circulation,
- its interaction with various body tissues when deposited,
- and its autoantibody activity.



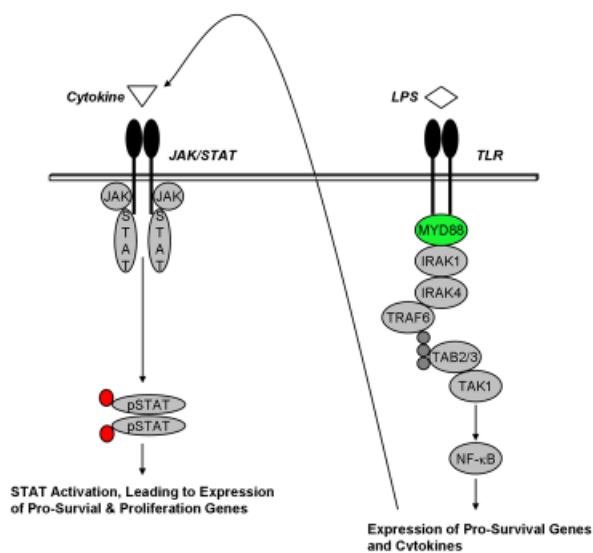
Slide 8 - Waldenström macroglobulinemia: Monoclonal IgM

The second major part of the diagnosis is the detection of the monoclonal IgM protein that's in the blood. This is often the way in which things are picked up right from the start. Many times, people might go in for a blood test, maybe just a common CBC type blood test for blood cell numbers and they'll be noted to be slightly anemic or they'll be noted to have the cells clump together or they'll be noted that the sedimentation rate, the speed at which cells come together, is increased. And more testing will be done including a protein electrophoresis and what that means is the various proteins in the blood stream are then analyzed and when they do that, they will see that there is way more of this IgM protein in the blood than there should be.

And secondly, of the IgM rather than lots of different type that would react against different proteins and viruses, etc. a lot of the protein is all identical, that's what the monoclonal part means. And again, this is one of the ways in which a diagnosis is made but this is also one of the issues that can cause a lot of symptoms because as I mentioned before this is a big protein, very sticky, thickens the blood and this then relates to a lot of the symptoms that can be seen.

We'll go through some of these now in a minute but the main three characteristics of this is that this can interfere with circulation, this can allow, this protein can actually deposit and stick to body tissues and cause those body tissues to malfunction and also it can stick red cells and other cells to each other and when it does that that can cause what we call hemolysis or breakdown particularly for example, of red cells.

MYD88 Mutations in Waldenström macroglobulinemia



Slide 9 - MYD88 Mutations in Waldenström macroglobulinemia

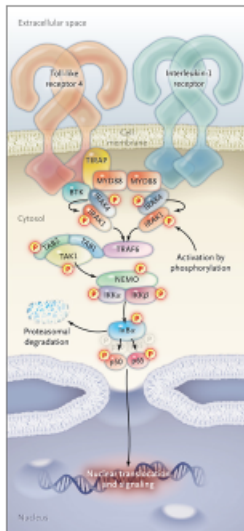
One last word here just talking about the mutational studies. So, you might remember we spoke about MYD88 as a mutation that is tested for and I mentioned that this can cause the protein, this MYD88 protein, to be abnormal and when it's abnormal it actually becomes hyper functional. So, this is just a little schematic that explains how that works. So again, I mention the proteins that are on the outside of cells. So, this TLR that you see here is called a toll-like receptor and there are a variety of different toll-like receptors. There are also other what we call cytokine receptors, and these are all ways in which the cell obtains information from outside and kind of tells us what the risks and messages from the environment may be.

Information is transmitted through this cascade of different proteins which is a little bit like the wiring in the cell if you like. The MYD88 is a protein that's right at the start of this whole messaging system and when that is mutated or changed, it's a little bit like a megaphone.

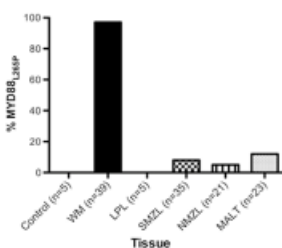
So, when it does that this becomes a very loud message and when it becomes very loud it activates a lot of genes that then sort of create this feedback loop where the message is going around and around and around. I sometimes mention sort of as, as an analogy people will sometimes think about maybe someone at the door ringing the doorbell repeatedly just sort of ding, ding, ding, ding, endlessly and everyone in the household becomes more and more kind of frustrated by all of the noise and everything becomes quite hyperactive and disrupted.

You can imagine that's what's happening here. These cells are now becoming overstimulated, they start growing more than they should. They make way more protein than they should, and the entire system becomes very revved up and very amplified. That's how the MYD88 mutation impacts this whole disease.

MyD88 L265P mutations are almost universal in Waldenström macroglobulinemia



- Whole genome sequencing in 30 patients – MYD88 L265P mutation found in 27/30.
- High frequency confirmed in 49/54 additional cases (91%)
- Rarely expressed in myeloma, MZL, or IgM MGUS

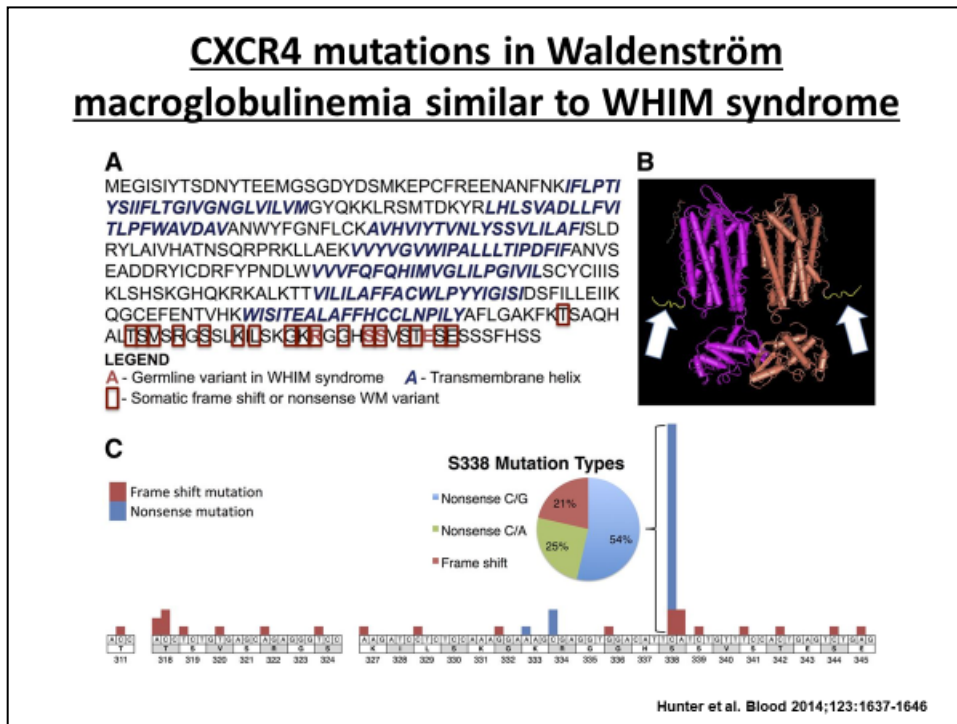


Treon SP et al. N Engl J Med 2012;367:826-833.
Ansell et al. Blood Cancer J. 2014 Feb 14;4:e183.

Slide 10 - MYD88 L265P mutations are almost universal in Waldenström macroglobulinemia

Again, as I mentioned before there been a number of studies that have looked at how relevant this is in Waldenström macroglobulinemia. Firstly, the initial study done by Steve Treon's group from Dana-Farber showed that this was a genetic finding that was present in about 90% of patients. Other groups including ours have done some additional studies that have looked at a variety of different and similar kinds of diseases and shown that really the Waldenström macroglobulinemia is the group where a very high percentage of them have the mutation. Other sort of similar diseases but that aren't Waldenström macroglobulinemia have much lower levels.

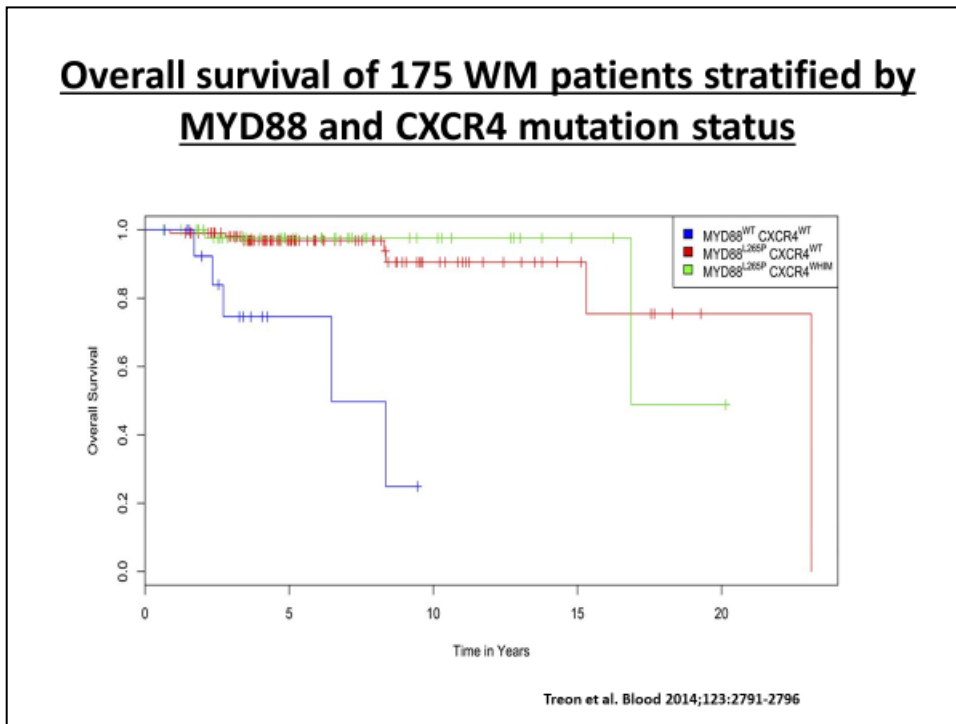
What's interesting again, you can see lymphoplasmacytic lymphoma but if they don't have the protein you can see that that's much less common when the protein is very increased the IgM protein, that's when the mutation is commonly seen. Marginal zone lymphoma and MALT lymphomas are very close cousins to Waldenström macroglobulinemia but many of them do not have this protein. So, it's a very useful test number one, in confirming the diagnosis and as we'll talk about in a minute also in determining the best treatment and the likelihood of benefit from that treatment.



Slide 11 - CXCR4 mutations in Waldenström macroglobulinemia similar to WHIM syndrome

The other mutation that will commonly be tested for right at the time when patients are diagnosed is this CXCR4 mutation. So, this was originally described in a disease called WHIM syndrome and this has to do with a type of syndrome where people have problems with their immune system because this homing device is entirely disrupted. So similarly, in about a third of patients one can see the CXCR4 mutation problem seen in Waldenström macroglobulinemia. And again, this is something that is starting to be done more routinely because particularly some of the newer therapies maybe more or less effective depending on whether the CXCR4 mutation is present in patients.

I would stress though that if you are a patient who has been diagnosed with Waldenström macroglobulinemia but you don't necessarily know whether the MYD88 mutation or the CXCR4 mutation has been done, I don't think it's an absolutely critical piece of information because most of the time we can make a definitive diagnosis without it. I would also say that even though it may have an association with higher or lower responses, it doesn't mean that if you go on treatment with for example Ibrutinib, that you wouldn't respond if you had a mutation or didn't. So, I think we're learning how to use this mutational status and so I think it's useful and interesting but not critical.



Slide 12 - Overall survival of 175 WM patients stratified by MYD88 and CXCR4 mutations status

This just highlights why that maybe the case. This is a 175 patients with Waldenström macroglobulinemia stratified by whether they were MYD88 mutated or CXCR4 mutated and you can see that it seemed like the wild-type group that you can see here -- in other words, these are the people that don't have mutations, they may have a little bit less in the way of favorable outcome compared to the folks that have these mutations.

I think what's interesting is as I showed you a slide or two before, is that many of these people might actually not have true Waldenström. They may be some of these other types of close cousin types of lymphoma. So, I think although is important and interesting and we're learning more, this may not necessarily be an absolute critical piece of information to work out right off the bat. But as you will hear more and more about Waldenström you'll know that this is something that's gaining a lot of favor and a lot of focus.

Waldenström macroglobulinemia – presenting symptoms

- 217 patients with serum monoclonal IgM protein ≥ 3 g/dl and $> 20\%$ bone marrow involvement -
 - Asymptomatic (27%)
 - Anemia (38%),
 - Hyperviscosity (31%),
 - B symptoms (23%),
 - Bleeding (23%)
 - Neurological symptoms (22%)

García-Sanz et al. Brit J Haematol. 115: 575-582, 2001

Slide 13 - Waldenström macroglobulinemia – presenting symptoms

What I hope you heard in this previous section was some data about how we diagnose the disease and important just again to stress that to have Waldenström you need two components. You need the high IgM protein in the blood and the lymphoplasmacytic infiltrate in the bone marrow or other organs.

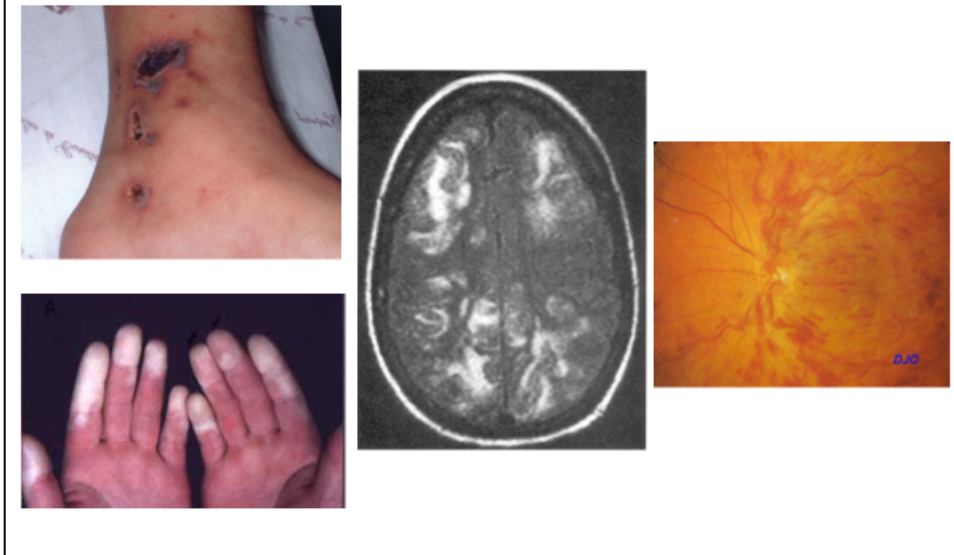
So, the next key question is will the average patient who has this disease, what do they show up with when they present to the doctor for the first time? And this was a study of just over 200 patients who, had a high level of serum IgM, note over 3 g, and at least 20% involvement by Waldenström of the bone marrow. And they went through each of these cases and determined what sort of symptoms they had, and I think it's interesting to note that just over a quarter of patients had no symptoms at all.

This was an incidental pickup as part of maybe some general physical exam type blood testing. About 40% of patients had some degree of anemia, a third of patients had problems with hyperviscosity, so this is where your protein in your blood is making the blood thicker than it needs to be and that causes the blood to be pumped with more difficulty causing a lot of symptoms. What are called B symptoms or what we call constitutional symptoms, and these are things like fevers or sweats or weight loss.

So important to know that this is not just feeling a little hot, these are sort of fevers of at least 101 or higher that have been documented. These are people that have drenching sweats most typically at night time so much so that they need to change their bedding or change what they're wearing at night and these are people that lose at least 10% of their body weight. So simply feeling a little hot and sweaty would not be a B symptom.

One of the things that's interesting about this higher level of IgM protein is that this can cause extra bleeding or very easy bleeding. So, people would notice that when they brush their teeth they really have really excessive bleeding from their gums, they may have bleeding in other places. And about 20% of patients had neurological symptoms and this would commonly be they just had difficulty thinking well, they've sort of seemed foggy, often their spouse would say they're really just not the person they were, maybe a number of months before. I think overall though important to see the broad spectrum of symptoms with which patients may present.

Hyperviscosity due to Waldenström macroglobulinemia



Slide 14 - Hyperviscosity due to Waldenström macroglobulinemia

I want to highlight now some of the symptoms and exactly what these things look like so that folks would have some idea of the spectrum of the disease with Waldenström's macroglobulinemia. So, the first issue is to mention hyperviscosity so as I said the IgM protein is a large molecule made up of five antibody molecules stuck together and this makes your blood a lot thicker than it should be so when it does that, circulation is significantly limited.

So, you can see here the problem with poor circulation causing the patient to develop ulcers on their leg. Here is what was called Raynaud's phenomenon, so you can see this person has very white fingertips and what happens is that really the circulation to the tips of the finger are quite restricted causing these fingers to become very white as shown here.

Here you can see a scan of somebody's brain and you can see this kind of white sort of matter that you can see sort of this white pattern through the brain. These are areas where blood flow is less than optimal and so because of that, the brain is kind of under some degree of strain and often will become a little more kind of swollen in these areas and this is what causes people to have significant difficulty with their thinking.

And many times, people may have trouble with their vision and this is shown here. You can see this is a shot taken into the back of the eye and you can see some of these little blood vessels here have almost much more puffy appearance and sort of swollen up, they call it sausageing where the blood is so thick it's almost like treacle as it gets pushed through sort of thick, blood that causes the blood vessels to get strained out like that. And then it causes a little bit of bleeding like you can see in this sort of speckled areas here. All of that really can interfere with people's vision. So, some of the features of hyperviscosity are difficulty seeing, difficulty thinking straight, difficulty with white fingers and areas of poor circulation and sometimes ulcers is highlighted in these cases.

**IgM deposition due to Waldenström
macroglobulinemia**

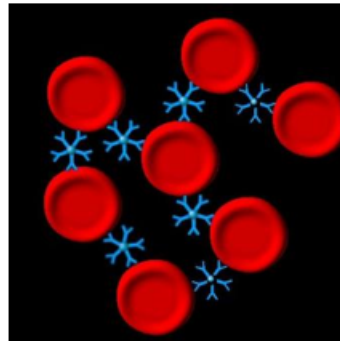
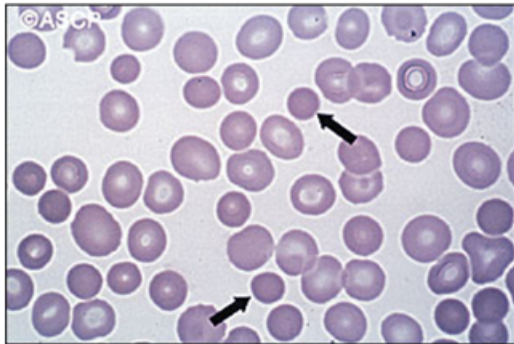


Slide 15 - IgM deposition due to Waldenström macroglobulinemia

The other problem that I mentioned before is that many times this very sticky protein, has a propensity to stick to tissue. So, if you look carefully at this person here below their knees you can see this patient has lots of kind of little dots if you like, little lumps that you can see in the tissue and this is the IgM protein actually being deposited in the skin. And if you look carefully here where you see these arrows you can see this green material that's in between the areas inside this tissue that you can see right here.

So this deposition can be a real problem because it can cause what we call amyloidosis or this can cause problems with just the protein itself being deposited and when it does that people can have difficulty with kidney function, can have difficulty with nerve function, sometimes even with cardiac or heart function because this extra protein stretches the tissue out and causes the tissue to not work in the way it should. In your skin it's a little less concerning, it's more annoying than concerning but if it's in your kidneys or in your heart or in your nerves you can have a lot of complications and symptoms.

Autoimmune hemolysis secondary to Waldenström macroglobulinemia



Slide 16 - Autoimmune hemolysis secondary to Waldenström macroglobulinemia

A further problem is the fact that this very sticky protein may not stick to tissues outside of the blood vessel but may stick to structures and things inside the blood vessel. So here is a cartoon of what's happening. These are red blood cells and you can see this five antibody or five what we call a pentamer antibody sticking to various red cells.

The problem when that happens is that the spleen is designed specifically to take out things that have antibodies on them. So, the spleen will rapidly break down all of the little macrophages which are the trash collectors within the cells or within the spleen, will take bites of the red blood cells as they go by. And you can see here these are red blood cells that have been kind of chomped as it were as they've gone through the spleen and are much smaller because parts of them have been chewed off and you can see these smaller cells are part of this what we call hemolytic process. So, this causes your hemoglobin to drop down and you to become anemic because the cells are being broken down.

Diagnostic Criteria for Waldenström macroglobulinemia

Waldenström macroglobulinemia

IgM monoclonal gammopathy (regardless of the size of the M protein) with >10% bone marrow lymphoplasmacytic infiltration (usually intertrabecular) by small lymphocytes that exhibit plasmacytoid or plasma cell differentiation and a typical immunophenotype (surface IgM⁺, CD5⁻, CD10⁻, CD19⁺, CD20⁺, CD23⁻) that satisfactorily excludes other lymphoproliferative disorders, including chronic lymphocytic leukemia and mantle cell lymphoma

IgM MGUS

Serum IgM monoclonal protein level <3 g/dL, bone marrow lymphoplasmacytic infiltration <10%, and no evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly

Smoldering Waldenström macroglobulinemia (also referred to as indolent or asymptomatic Waldenström macroglobulinemia)

Serum IgM monoclonal protein level ≥3 g/dL and/or bone marrow lymphoplasmacytic infiltration ≥10% and no evidence of end-organ damage, such as anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly, that can be attributed to a lymphoplasmacytic proliferative disorder

Kyle et al. Leukemia. 2009 Jan;23(1):3-9.

Slide 17 - Diagnostic Criteria for Waldenström macroglobulinemia

What is important though, as you can tell with what I've just presented is that there is a broad spectrum of different people that have different, sort of stages of the disease. In other words, some people can have lots of problems and some people can have very few problems. So, to try and really categorize that you can think of Waldenström macroglobulinemia in three broad categories.

There are some people which we called and IgM MGUS or monoclonal gammopathy of uncertain significance which basically means they picked up on the IgM protein, it's at a low level. They found only a small amount of lymphoplasmacytic infiltration in the bone marrow but patients otherwise are in very good health with no symptoms and this is a protein problem that may not actually really turn into a very symptomatic problem over time.

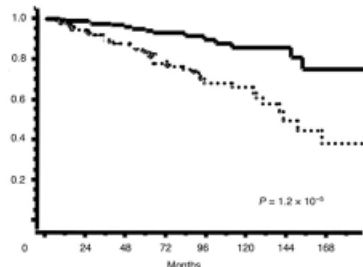
There is a second group of what we call smoldering Waldenström macroglobulinemia and these are people that have a little bit more in the way of trouble. The protein may be higher, the infiltration in the bone marrow may be greater but they still don't have much in the way of symptoms or virtually any symptoms where it shows end organ damage where it's actually causing problems at any of the sites I just mentioned.

Again, these patients may not need any treatment, or anything done immediately but these folks are a little bit more higher risk to turn into true Waldenström macroglobulinemia, which are people that have, now what we call end organ injury. So, we can see this involvement of the bone marrow by at least 10% of these lymphoplasmacytic cells but we can also then find a variety of other symptoms, some of the things that I just mentioned before.

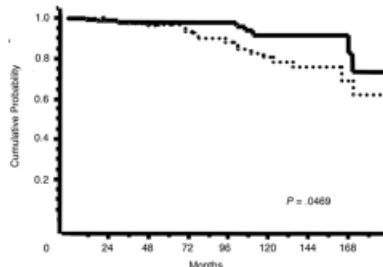
Important as I mentioned right in the beginning that it looks like Waldenström's based on the blood test, on the test on the protein on the outside of the cells that the pathologist will do as well as the genetic test and it isn't one of these other types of diseases.

Time to developing WM and Survival in patients with Indolent WM or IgM MGUS

Time to evolution



Overall survival



(— MGUS; ...IWM)

MGUS (217 patients) and indolent Waldenström's macroglobulinemia (201 patients) groups

Baldini L et al. JCO 2005;23:4662-4668

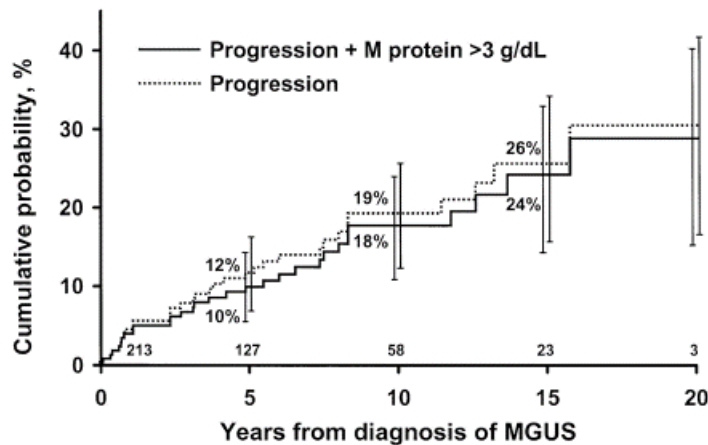
Slide 18 - Time to developing WM and Survival in patients with Indolent WM or IgM MGU

So, you might ask well, why does that matter? Well, shown here is what's the likelihood if you have this monoclonal gammopathy problem or if you have an indolent Waldenström's in other words, you don't really have any damage to your tissue, you don't have an anemia, you don't have low platelets, you don't have enlarged lymph nodes, you don't have any issues with the protein being deposited anywhere or causing neuropathy or anything like that.

If you look at that MGUS patient population and you look at the patients with the Waldenström's that is smoldering and then you look to see how do these patients do as far as the time to when they needed treatment or how long they lived, you can see that the patients do extremely well. Important to point out that this is in months and this is 10 years right over here.

So, what's important to notice is that patients with the IgM MGUS, about 80% of them still haven't required anything be done after 10 years in the study. A little bit more, more like 60% of the patients with smoldering Waldenström's still haven't required any specific intervention and as you can tell out of this period of time if you look at how these patients are doing as far as have any of them passed away, you can see that a very small minority of patients have actually passed away from this disease. So, the reason for stressing that is just not everybody that has a detectable IgM protein and not everybody that finds this lymphoplasmacytic lymphoma in the bone marrow immediately requires treatment because these people were not treated at all.

Risk of progression from IgM MGUS to WM or another B-cell malignancy



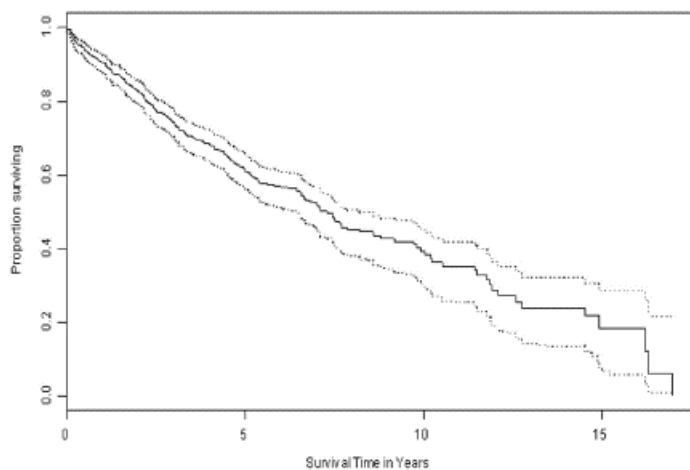
The overall average risk for progression is approximately 1.5% per year.

Kyle R A et al. Blood 2003;102:3759-3764

Slide 19 - Risk of progression from IgM MGUS to WM or another B-cell malignancy

This just tells you what's the likelihood of that IgM MGUS actually becoming Waldenström's or developing into some other kinds of lymphoma and you can see here again out at 20 years that's about 30% of patients. So important to notice that 70% of patients didn't actually turn into anything. So that's why we take the time and trouble to work out which category you're in because if you have a very low amount of protein and not much in the way of symptoms, observation is or watching and waiting is a very reasonable plan.

Survival of 587 symptomatic patients with Waldenström macroglobulinemia



Morel P et al. Blood 2009;113:4163-4170

Slide 20 - Survival of 587 symptomatic patients with Waldenström macroglobulinemia

In contrast, this highlights the patients that had a lot of symptoms at the time that they presented. Now I have to stress that this is probably changing because this is a slide that is almost 10 years old. This really needs to be

updated with a new study but almost 600 patients who had lots of symptoms, they look to see how did these people do over the course of 15 years. And you can see that unfortunately many of them ran into trouble and many of them passed away over time due to the fact that the Waldenström's actually became a significant complication and problem in their lives.

Now I would stress there are a number of new drugs that I'll talk about in just a minute that were not available in 2009 and that has definitely changed the slope of this curve. So, my prediction is that the slope of the curve is much more improved and is kind of more in the likelihood of 10 to 15% or maybe even higher better than this slide appears but we still need that data to be published for us to know that for a fact.

Who needs treatment?

Slide 21 - Who needs treatment?

So, the next portion of the discussion is to say well, based on the fact that now we clearly understand what Waldenström macroglobulinemia is, we have a clear understanding of what needs to be done as far as testing, etc. is concerned. We have a clear understanding of what are the symptoms that one can present with and we now know that they can be sort of three large categories of patients with Waldenström macroglobulinemia.

The question then comes up, well, who exactly needs to get treated?

Patient 1

- 66 year old man
- Went for an executive physical – in good health with no symptoms
- Found to be mildly anemic (Hgb 12.8g/dl). Other blood counts – normal
- Also noted to have increased total protein with an increased gammaglobulin level.
- Monoclonal IgM – 1.4 g/dl
- Bone marrow biopsy – 20% involvement by lymphoplasmacytic lymphoma
- CT scan – no lymph nodes

Slide 22 - Patient 1

I want to highlight two patients here and just for us to contrast the fact that some patients may need treatment right away and some patients do not. Patient number one is a 66-year-old man who went in for his executive physical which he has once a year, feeling that he was in good health with no symptoms but was found to be slightly anemic which was a change from a year before. Everything else that was done was found to be normal.

But his conscientious doctor felt that it was important to understand why he was anemic and as part of the testing added a serum protein electrophoresis to take a look at the proteins in his bloodstream and noted that the gamma globulins so these are the immunoglobulins, the Ig -- IgM fraction was increased and then did some additional testing to work out which one and show that it was a monoclonal IgM protein and it was typically would be more in the 300 mg range, this is 1400 mg in his case -- went ahead and did a bone marrow test and showed about 20% involvement by lymphoplasmacytic lymphoma.

So really making a definition because this is more than 10% and a monoclonal protein is detected, of this being Waldenström macroglobulinemia but no lymph nodes were noted when a CT scan was done.

Patient 2

- 67 year old man
- Severe fatigue, nausea, visual difficulties, increasing confusion and sleepiness, gums bleed easily.
- Anemic (Hgb 8.8g/dl). Platelets decreased to 96,000.
- Ulcers have developed on his ankles
- Monoclonal IgM – 6.6 g/dl. Viscosity – 5.8
- Bone marrow biopsy – 85% involvement by lymphoplasmacytic lymphoma
- CT scan – enlarged liver and spleen and multiple bulky lymph nodes in the abdomen

Slide 23 - Patient 2

In contrast here is patient number two. He's 67 years old, he's really not been feeling particularly well, has been very fatigued, has had some nausea problems, noted difficulty was reading, his wife has noted that he is significantly confused compared to his usual self. He's very sleepy and every time he brushes his teeth they bleed very easily. His gums bleed very easily.

He sees his doctor and bloodwork shows quite a bit of abnormalities. He's quite anemic with a hemoglobin of 8.8 g/dL, his platelet count which should be 150,000 or higher is decreased at 96,000. He's had this ulcer on his ankle that won't heal and when his doctor does testing it shows a very high IgM level at 6.6 g/dL. We can then do a testing for viscosity to see if the viscosity shows the blood to be thickened, 5.8 is a significantly high number, much more typical for normal would be about 1.5. He has a bone marrow test done which shows 85% involvement of the bone marrow by lymphoplasmacytic lymphoma. When a CAT scan is done he shows multiple lymph nodes that are enlarged and his spleen and his liver show that there enlarged as well.

Many treatment options

- Watch and wait
- Single agent rituximab
- Chemoimmunotherapy combinations
- Ibrutinib
- Plasmapheresis
- Clinical trials with new agents
- Stem cell transplantation

- **Which approach is best?**

Slide 24 - Many treatment options

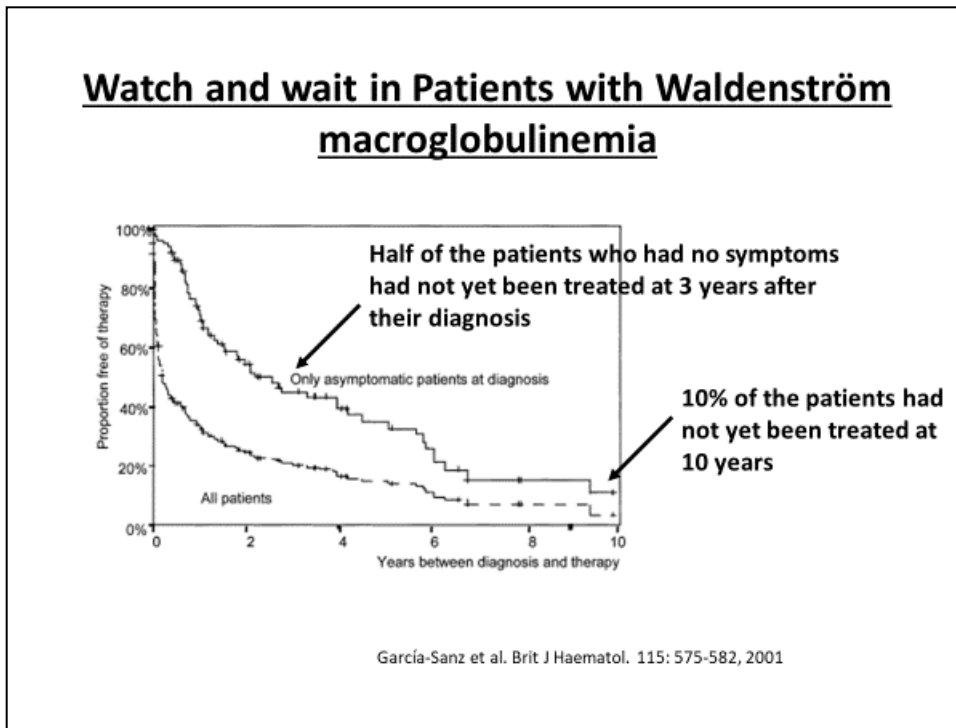
So, clearly these are two very different patients. Patient number one will not need any treatment. Patient number two will definitely need treatment. So, when one reads the literature or talks to your doctor you'll know there are many treatment options available and I've listed a whole bunch of them here. The key question is which approach is best. So, what I would like to do is talk through some of the treatment approaches and why and when we would consider doing them.

Does everyone need treatment at diagnosis?

Slide 25 - Does everyone need treatment at diagnosis?

So, the first main question that touches on what we've discussed already and that is does everyone need treatment immediately when you are diagnosed? The reason I showed some of that previous data is to highlight

that in fact you don't always need treatment right away and this has been something that's been helpful for me is just to see these are patients who underwent a watch and wait approach with Waldenström macroglobulinemia.



Slide 26 - Watch and wait in Patients with Waldenström macroglobulinemia

Now again just to highlight this is pretty old data so some of these results may even be better than now. But if one looks at all patients and if you look specifically here at the patients who did not have symptoms at the time they were diagnosed, and they were watched, you can see that at least half of them did not need any treatment, even when you got out to around three years. And in fact, 10% of those patients had not received any treatment by the time you got to 10 years. So again, these are patients who clearly met the criteria for Waldenström macroglobulinemia but did not have symptoms and again just to stress that watching and waiting can be often achieved and can be continued for a prolonged period of time.

What clinical findings suggest that treatment should be started?

- Fever, night sweats, or weight loss.
- Lymphadenopathy or splenomegaly.
- Hemoglobin ≤ 10 g/dL or a platelet count $< 100 \times 10^9/L$ due to marrow infiltration.
- Complications such as hyperviscosity syndrome, symptomatic sensorimotor peripheral neuropathy, systemic amyloidosis, renal insufficiency, or symptomatic cryoglobulinemia.

Kyle et al. Semin Oncol. 2003 Apr;30(2):116-20

Slide 27 - What clinical findings suggest that treatment should be started?

This next issue is just to say well, what exactly would be criteria that would say a patient needs to get treatment and there have been a number of workshops that have been held over time where experts in the field have met together and have spoken about what they feel are key criteria for considering treatment. And these are some of the ones that have are felt to be important to consider treatment because they're clearly a reflection of the fact that the disease is behaving badly.

So, remember we spoke about the symptoms, the B symptoms or constitutional symptoms and if those are present that often tells you that the lymphocytes are very activated and when they are activated that's what is causing these symptoms and that would suggest that the patient may be need to be treated sooner rather than later.

So, this is a fever of greater than $101^{\circ}F$, patients with drenching night sweats requiring you to change what you're wearing or more than 10% of your body weight has been lost over a period of six months. If the lymph nodes are starting to enlarge, the spleen or the liver are starting to enlarge, the cells are accumulating outside of the bone marrow that would be a reason to start treatment.

If patients like the second patient and I presented is starting to become very anemic, so normal would be more in the 13.5 g range but you can see 10 is very typically a cut off for considering treatment, platelet should be 150, this is 100. Again, as reflected in patient number two both of these would suggest the bone marrow is being replaced by these cells and when that's the case that may be a reason to start treatment. And then complications, as I showed you when patient start to have places where this protein is beginning to be deposited and it's interfering with function so that people are getting the hyperviscosity problem, they're starting to get neuropathy, so the protein is interfering with the function of nerves. Systemic amyloidosis is again deposits of the protein but with inflammatory changes that happen at the same time and that then causes trouble with your kidney or your heart and you can see kidney function specifically listed here or cryoglobulin anemia is where the protein is starting to interfere with circulation and particularly that's associated with being very sensitive to cold. These are all reasons to say we need to do something to bring the protein down or to clear out the amount of involvement of the bone marrow or lymph nodes or spleen.

Very important to notice here is IgM level is not mentioned and I think it's important to recognize that exactly at what point the IgM level will affect a patient is very variable. We clearly don't like it to become extremely high, but few patients really have much in the way of symptoms when they are under 3 g/dL. So important that we don't just base it on the blood test and the level of IgM, it's based on the whole patient and the symptoms they may be experiencing.

**Before starting therapy –
Does the patient have hyperviscosity and
do they need plasmapheresis?**

Slide 28 - Before starting therapy – Does the patient have hyperviscosity and do they need plasmapheresis?

One important question that your doctor will ask is before starting treatment does the patient have hyperviscosity and do they need plasmapheresis? So hyperviscosity is again when the blood is very thickened and many of those symptoms like difficulty with vision or thinking straight or some of the other issues that we spoke about are now present. Plasmapheresis is where the blood is essentially washed if you like. You would be hooked up to a machine and the plasma is replaced with saline to really kind of dilute out this very high level of IgM in the blood.

Plasmapheresis for Waldenström patients with hyperviscosity

- Symptoms of hyperviscosity –
 - Visual deterioration
 - Neurological symptoms
 - Bleeding
- Rarely seen with IgM <4g/dL

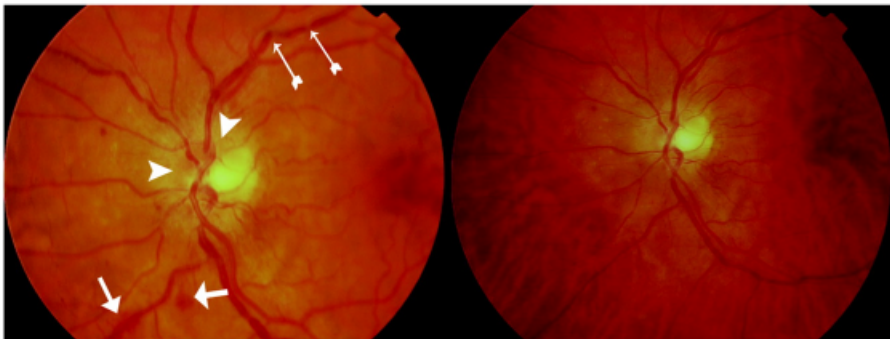
Slide 29 - Plasmapheresis for Waldenström patients with hyperviscosity

So, the reasons that we would consider doing plasmapheresis are listed here. If people have the symptoms of hyperviscosity so I mentioned visual deterioration, neurological symptoms or bleeding often with very high IgM levels and often the lab testing for viscosity is significantly increased but importantly this is really uncommon when you have a IgM level of less than 4 g or less than 4000. But the reason it matters is some of the antibody treatments like the use of rituximab may sometimes make the IgM go up before it comes down and if you're IGM level is already high and you have viscosity problems, that could make things a lot worse. So, it's important to first kind of wash the blood as it were before starting the treatment.

Efficacy of Plasmapheresis for Waldenström patients with hyperviscosity

Before Plasmapheresis

After Plasmapheresis



Before plasmapheresis - optic disc edema (arrowheads), central retinal hemorrhages (bold arrows), and venous "sausaging" (thin arrows).

Menke et al. Invest Ophthalmol Vis Sci. 2008Mar;49(3):1157-60.

Slide 30 - Efficacy of Plasmapheresis for Waldenström patients with hyperviscosity

Just to highlight here that this is a very effective therapy. Remember I showed you a patient before who had very expanded blood vessels. As you can see this is on the back of the eye, you can see some kind of blanching or very white appearing optic disc. You can see some of this extra redness here where the person is having some bleeding in their eyes. So, this is some of the sausaging that we mentioned, some of the retinal hemorrhages and the optic nerve which is now very edematous or swollen.

And this is after plasmapheresis and you can see all of these issues have rapidly improved. So, this is a very effective therapy, but I have to stress this is somewhat of a metaphorical Band-Aid because all it does is it just skims off the protein, but it doesn't fix the underlying problem. So, one needs to move on to more definitive treatment than simply clearing out the blood stream.

**Initial treatment for untreated
symptomatic WM patients**

Slide 31 - Initial treatment for untreated symptomatic WM patients

So, what is that treatment? So, the initial treatment for untreated, for patients that are symptomatic, so I stress the symptomatic because I think hopefully you've understood that not everyone may need treatment right away.

Common Treatments used as initial therapy for WM

- Purine analogue based combinations –
 - FCR/FR
- Alkylating agent based combinations –
 - R-CHOP
 - DRC
 - R-Bendamustine
- Bortezomib based combinations –
 - BDR
- Rituximab alone
- Ibrutinib

Slide 32 - Common Treatments used as initial therapy for WM

And there are many therapies, I've listed a variety of them here, sometimes the treatment is based on a purine analog. This is something that's not as commonly used anymore but fludarabine was a very commonly used drug maybe 10 years ago and used in combination. It's very effective but it does have some troubles with increasing the likelihood for transformation or bone marrow damage.

More typically is the use of an alkylating agent, so chemotherapy treatments like R-CHOP or the DRC regimen, which is a steroid and rituximab and cyclophosphamide, newer treatment is with bendamustine with rituximab so those are alkylating agent combinations and are very effective.

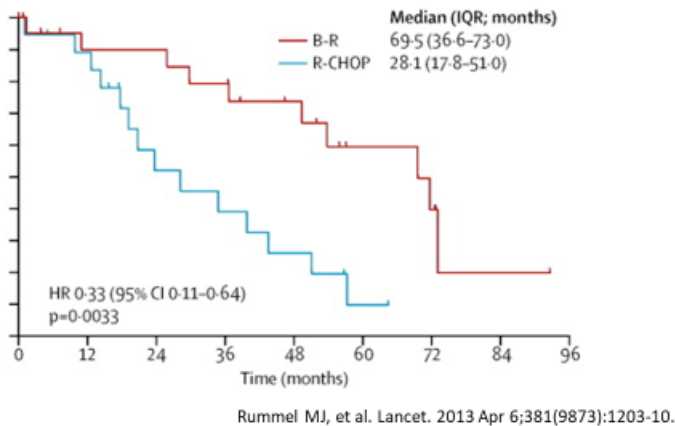
There's a proteasome inhibitor which basically interferes with the protein production. Clearly if you interfere with the protein production and poison the cell by trapping the protein in the cell causing toxic breakdown products to heap up inside the cell that'll cause the cell to die off and so bortezomib with rituximab and sometimes with steroids has been very effective.

Particularly in patients with neuropathy the use of rituximab, this is an antibody treatment, it goes after CD20 you might remember I mentioned proteins on the outsides of cells, this would actually attach to that. You might remember I mentioned the spleen hates antibodies stuck on cells, so actually you've kind of use this antibody to turn the immune system on the cancer cell and this can be very effective. However, the challenge here is that sometimes it'll make the protein go up before it comes down as these cells release the protein as they die.

Going to talk a little bit more about Ibrutinib. This is a BTK inhibitor, Bruton's tyrosine kinase inhibitor. The messaging system coming into the cell also comes through what's called the B cell receptor and that is on a permanently switched on basis. By cutting the cord and stopping that signaling, Ibrutinib has been shown to be very effective particularly when MYD88 mutations are present.

Bendamustine plus rituximab compared with R-CHOP in WM patients

- A subset analysis in the prospective randomized STIL trial - bendamustine plus rituximab (BR) compared with R-CHOP



Slide 33 - Bendamustine plus rituximab compared with R-CHOP in WM patients

So, I want to just highlight a little bit of the information to say why do we choose these regimens. So, you -- I mentioned alkylating agents and Bendamustine is a treatment of choice in combination with rituximab. In a larger study in low-grade lymphomas this was compared to R-CHOP chemotherapy, this is the subset analysis of patients who had Waldenström's, but you can see here in the red line people receiving Bendamustine plus rituximab had a much longer time and longer benefit from therapy than those who received R-CHOP chemotherapy. So, both of these are effective regimens but Bendamustine appeared in this study to have the edge and have a better outcome as far as durability of benefit is concerned.

Rituximab alone for Waldenström macroglobulinemia

69 symptomatic WM patients – rituximab x 4 doses

ORR 52% - 27% PR, 25% MR

Median duration of response – 27 months

Gertz et al, Leuk Lymphoma. 2004 Oct;45(10):2047-55.

Same study – evaluated IgM levels for “flare”

54% had an increase in IgM

27% still elevated at 4 months

No factors predicting an increase in IgM levels could be identified.

Ghobrial et al. Cancer. 2004 Dec 1;101(11):2593-8.

Slide 34 – Rituximab alone for Waldenström macroglobulinemia

I mentioned the use of this rituximab antibody on its own and again just to stress the fact that this is an effective therapy, very well tolerated. However, the response rates are a little bit lower because you don't have any chemotherapy here, it's just an antibody treatment and in the same study when they looked at this flare phenomenon, about half the patients had an increase in IgM and it took quite a long time to come down.

So, I think very important for people to be aware of that and to recognize that if the IgM is high to begin with one may be better off starting with a chemotherapy-based regimen than rituximab alone. Many times, in our practice we will give the chemotherapy part alone as the first cycle and add the rituximab only with second and subsequent cycles.

Ibrutinib in Waldenström macroglobulinemia

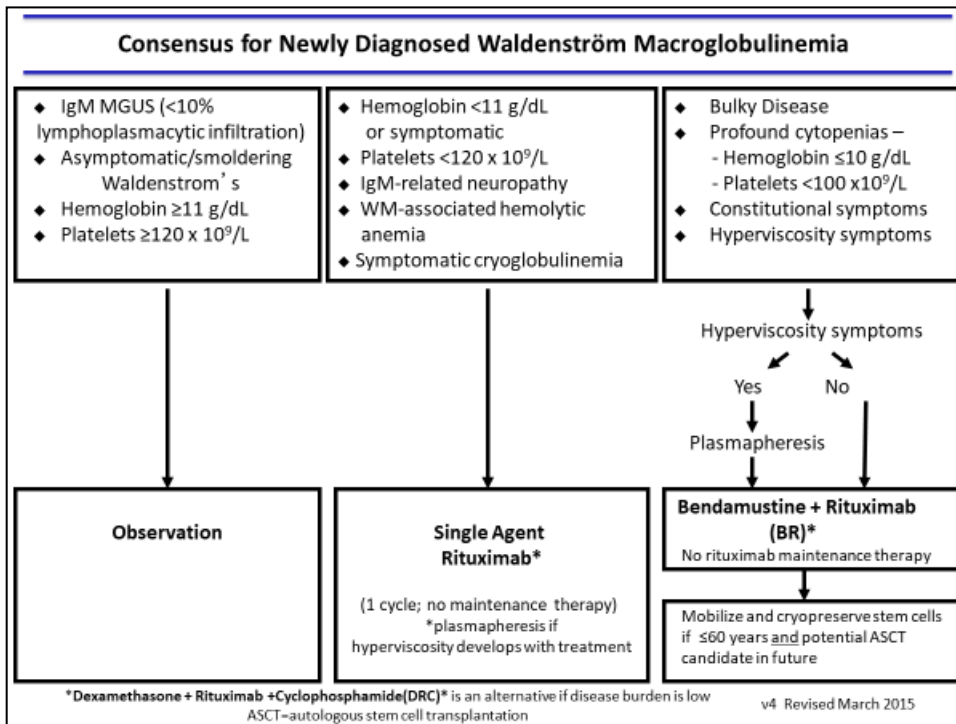
- 63 previously treated patients received 420 mg of oral ibrutinib daily for 2 years or until progression.
- ORR was 90.5%, with a major response rate (PR or better) of 73% and a median time to response of 4 weeks.
- 2-year progression-free and overall survival rates among all patients were 69.1% and 95.2%, respectively.
- Toxicities > grade 2 - thrombocytopenia; neutropenia; atrial fibrillation and epistaxis.

Treon et al. *N Engl J Med.* 2015 Apr 9;372(15):1430-40.

Slide 35 - Ibrutinab in Waldenström macroglobulinemia

I mentioned Ibrutinib, this is a new drug, one that has been very exciting and one that has excellent results. This was the original study published by the group from Dana-Farber utilizing this medication, it's a pill which you take every day. In this study people were taking it up to two years and beyond. I think what was very exciting about this is the response rate was very high, 90% of patients benefited, very similar to what we see with the Bendamustine type chemotherapy and it was important also to see that many of these patients have remained on treatment for an extended period of time.

The important thing here was that it was quite well tolerated but there are a few side effects, it does make your blood count sometimes go down a little bit, can cause easy bruising and bleeding, can cause some irregular heartbeats but again in comparison to chemotherapy is actually very well tolerated. The biggest challenges just the durability of treatment, this treatment is one that you have to remain on. As soon as you stop it the disease will reactivate again in contrast to chemotherapy such as Bendamustine plus rituximab where you can get 4-6 months of treatment and then be off treatment, hopefully for a prolonged period of time.



Slide 36 - Consensus for Newly Diagnosed Waldenström Macroglobulinemia

So, to try and guide folks as to what's the best strategy, our group at Mayo Clinic has put together kind of a consensus of how we like to treat patients and we try and highlight these three groups of patients. Remember, I mentioned the people where we just detected the IgM, the MGUS patients and these patients we don't recommend any treatment, we would recommend observation. In patients who really have some mild symptoms particularly those that have more in the way of problems with neuropathy or they're starting to have the red cells stick to each other, often the use of just the antibody rituximab can be very useful and we tend to give four doses over the course of a month once a week and then follow patients with no additional treatment.

In patients such as patient number two that we mentioned who clearly have very aggressive bulky disease and lots of problems where clearly treatment is needed, our first question is always is hyperviscosity present? If yes, then we will do plasmapheresis first. If no, we will proceed to treatment. Now there are many different treatment regimens that one can use but I want to highlight here our first choice and that's to use Bendamustine plus rituximab.

We typically will give at least four cycles in other words, two doses on day one and then on day two and then repeated four weeks later and we do that for four, maybe up to six rounds of treatment. We don't typically do Rituxan maintenance or rituximab maintenance. We prefer just to do the chemotherapy rituximab combination alone. You could consider other regimens here but that's the treatment of choice from our group. We often will in young patients consider collecting some stem cells and keeping them aside if the patient has a good response to this treatment. That's not something we would do for everybody, but it is something to think about.

Subsequent treatment in relapsed WM patients

Slide 37 - Subsequent treatment in relapsed WM patients

So with the last few minutes wanted to talk about well, what happens if you did all of that and you had an excellent result but a number of years down the line the disease started to get active and you started to notice the anemia creeping back and the platelets going down and the lymph nodes enlarging and the protein going up, all of it suggesting that it was time to do additional treatment to get the disease back under control?

Newer drugs with promise

- BTK inhibitors - ibrutinib
- PI3kinase inhibitors - Idelalisib
- mTOR inhibitors - Everolimus
- New anti-CD20 antibodies - ofatumumab
- Anti-bcl2 agents - venetoclax
- New HDAC inhibitors - panobinostat
- New proteasome inhibitors - carfilzomib
- New Imids - Pomalidomide

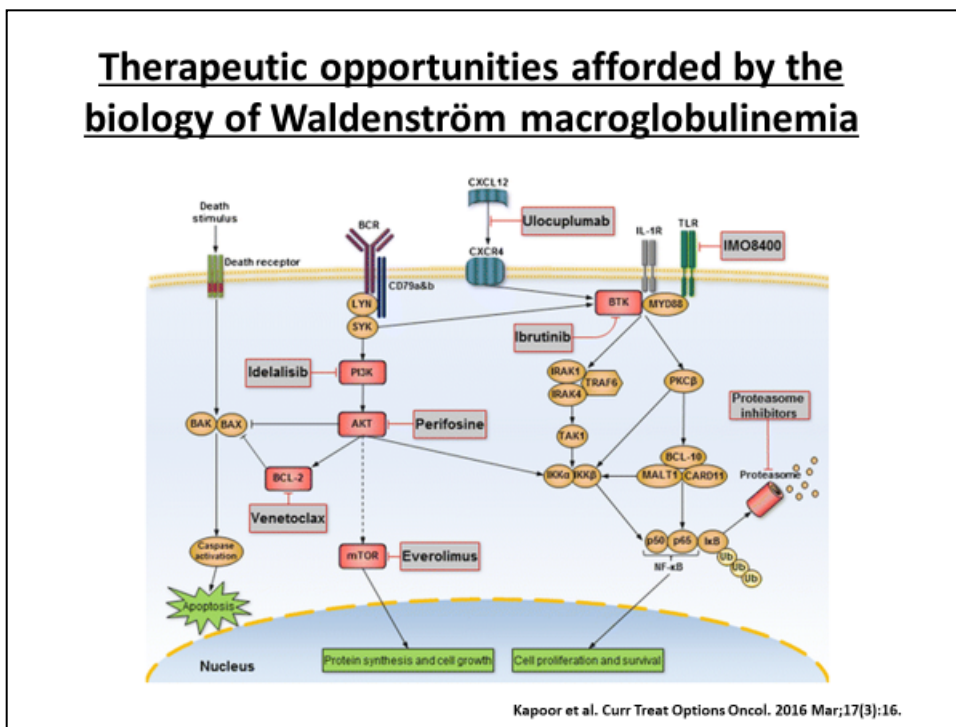
Slide 38 - Newer drugs with promise

Again, I want to encourage patients by saying there are a lot of drugs becoming available or already available for this disease. So, I mentioned Ibrutinib but other agents that mess with different pathways within the cell including blocking the Pi3 kinase pathway or the mTOR pathway all of those have shown a lot of significant

promise. CD20 is the target of rituximab but there are new anti-CD20 antibodies and those are also proving effective and promising.

A family of drugs that is very encouraging because it interferes with the death pathway, so the cells have a natural switch inside of them that will be switched on and the cell will die off as it has outlived its usefulness. The problem is that in Waldenström's the cells won't die like they should, so this treatment will actually trigger that. The drug is called venetoclax and is looking very promising in Waldenström's patients.

I mentioned bortezomib which is a pretty is a proteasome inhibitor and there are new ones in that class. There are drugs that change the immune system such as lenalidomide and a family member, pomalidomide is also being tested. And then there are other ways in which the DNA can be changed within a tumor cell in agents such as panabistat[sp] that can be used. So, this is a lot of different drugs, I don't mean to highlight each one of them with any more detail than just to say should the disease come back, patients should be encouraged that there are many options that could be considered.



Slide 39 – Therapeutic opportunities afforded by the biology of Waldenström macroglobulinemia

This just highlights how these different drugs work. So, there are really four main ways in which the cell is getting an advantage to grow. The first is that toll-like receptor, that is a way in which the cell speaks to the outside of the -- to its environment outside the cell. And when that happens here's MYD88, it activates this pathway and there are drugs that actually interfere with toll-like receptor signaling.

This CXCR4 protein I mentioned before because genetic mutations may matter but this tells the cell where to go and where to live and why it accumulates most times in the bone marrow. And there are now a number of antibody treatments that will target this particular receptor which will shut cells down. There's the B cell receptor pathway, this is really what makes a B cell a B cell and keeps it activated and causes it to make antibodies. And there are a variety of different drugs as you can see in these little squares here that will interfere with this pathway and Ibrutinib, the drug I just mentioned, will interfere with both this pathway and the toll-like receptor pathway this giving you almost a two-for-one benefit.

And then finally, there's this death stimulus called a death receptor. So, when the cell is supposed to be shutdown messages that come through, the death receptor would trigger death of the cell, but these cells are

very resistant to that and that's where the venetoclax treatment works to tip the balance in favor of shutting cells down.

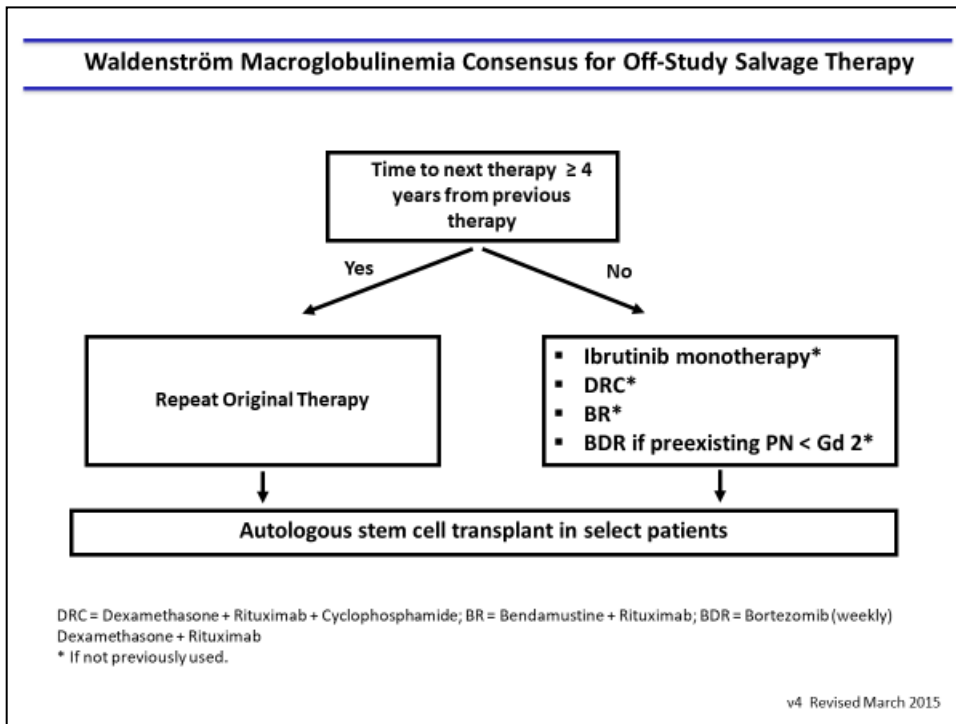
Ibrutinib in Waldenström macroglobulinemia

- 63 patients received 420 mg of oral ibrutinib daily for 2 years or until progression,
- ORR was 81% (4 VGPR; 32 PR, 15 MR), with a major response rate (PR or better) of 57.1% and a median time to response of 4 weeks.
- 59 patients remain on study with 7 on reduced doses of ibrutinib.
- Toxicities - thrombocytopenia; neutropenia; stomatitis; atrial fibrillation; diarrhea; herpes zoster; hematoma; hypertension and epistaxis.

Treon et al. ASH. 2013 Abstract 251.

Slide 40 - Ibrutinab in Waldenström macroglobulinemia

So, this just highlights a little bit more detail about Ibrutinib, which can be commonly used as a second-line agent and in fact this agent is approved both frontline and second-line but the reason I highlighted here is in our practice Ibrutinib is our first choice in the second-line. So, we commonly will use bendamustine plus rituximab as our first line, but we will go to Ibrutinib as our second-line. And again, just stressing the fact that initial studies showed a very high response rate and with follow-up those response rates have been shown to be even higher and the responses deepened if patients remain on the drug.



Slide 41 - Waldenström macroglobulinemia Consensus for Off-Study Salvage Therapy

So here is our consensus of how we would consider patients be treated if their disease comes back. So, if you were treated and you really had an excellent response meaning that more than four years you've been off all treatment, one could consider repeating the original therapy. This was a lot more popular when we had very limited options, this is becoming less popular now because there are so many other options.

So, in our practice we would commonly look to use Ibrutinib as our next step, but we would then consider the other regimens that I had mentioned before if you did not receive that regimen as the frontline. And in select patients we will consider doing an autologous stem cell transplant meaning using your own stem cells which we would collect, we would give a high dose of chemotherapy and then give the cells back as part of the whole transplant process. We don't usually recommend using somebody else's bone marrow because that has a lot of side effects and toxicity.

Transplantation in relapsed Waldenström macroglobulinemia.

Autologous transplant –

158 WM patients

Non-relapse mortality – 3.8%

5-year PFS – 40%

5-year OS – 68%

Kyriakou et al, J Clin Oncol. 2010 May 1;28(13):2227-32.

Allogeneic transplant –

86 WM patients (37 MAC and 49 RIC)

Non-relapse mortality – 33%(MAC), 23% (RIC)

5-year PFS – 56%

5-year OS – 62%

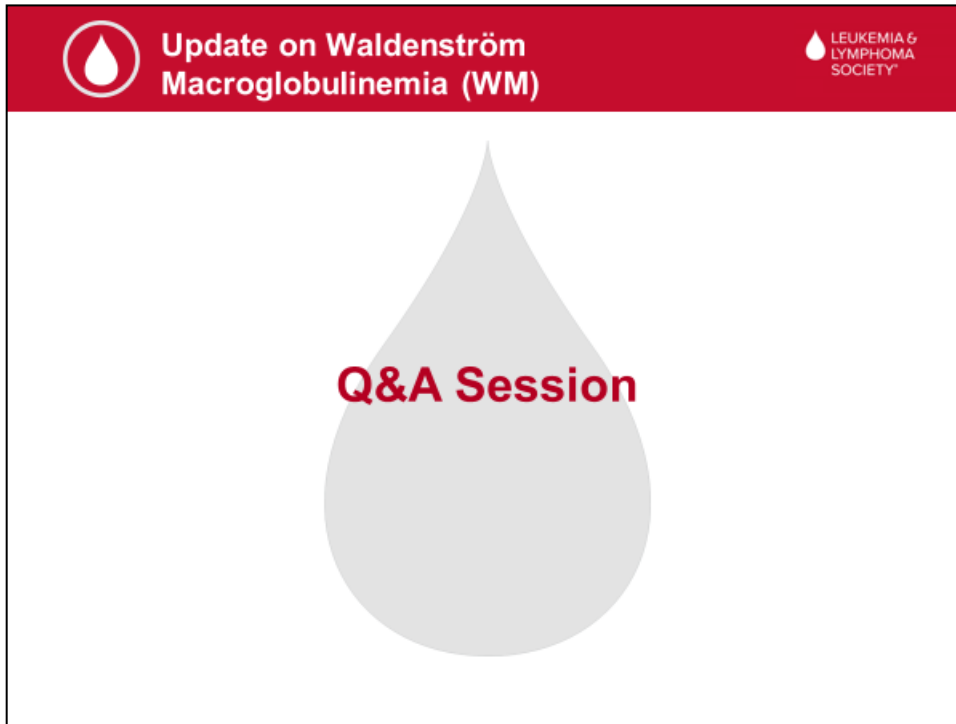
Kyriakou et al. J Clin Oncol. 2010 Nov 20;28(33):4926-34.

Slide 42 - Transplantation in relapsed Waldenström macroglobulinemia

So, the final thing just to say is here is a little bit of it data about transplantation in Waldenström macroglobulinemia, this is not done very commonly. So, as you can see these are both from various registries and the numbers are relatively small. An autologous transplant is where a high dose of chemotherapy is used, and your own stem cells are given back to you as a rescue and you can see that most patients did very well. This non-relapse mortality is how many people actually died from going through the transplant and you can see it was about 4%. And if you say well, how do people do with this about half of the patients actually didn't require additional therapy at the five-year mark. Important though to notice that still there are many of the people that go through this transplant process are quite sick and so a sizable proportion of patients may have passed away if the treatment didn't work.

This is an allogeneic transplant where somebody else's bone marrow is used, this could be a sibling or a matched unrelated person. Here this is a lot more risky. So, this is when you have a matched related donor with a, with the bone marrow being significantly ablated or beaten-down by the chemotherapy. This is when you have a reduced intensity transplant which has less immediate toxicity but unfortunately there is a risk for what we call graft versus host disease where the new bone marrow may actually attack some of your tissue and that's the main side effect and complication from a transplant process.

In our practice in patients where the disease is proving quite difficult to control we will consider an autologous transplant. We don't usually consider an allogeneic transplant again because there are so many other good and new options which we would consider instead. So, with that I like to thank you for your time. I'm going to close here and hand it back to our moderator and appreciate your time and attention. Thank you very much.



Slide 43 - Q & A Session

Lizette Figueroa-Rivera:

Thank you so much, Dr. Ansell, for providing us with this very important update and we do have questions that we have received from patients and caregivers alike that have contacted LLS through our online community or have spoken to one of our information specialists. And the first pre-submitted question is how did I get Waldenström's macroglobulinemia and is there a familial link?

Dr. Stephen Ansell:

So, there are two parts to that question and both parts are very important. The first part is how did you get it and the answer is we're not entirely certain. So, we can certainly see when you get it because as I mentioned the cells, the lymphoplasmacytic cells, begin to accumulate in the bone marrow, these cells are stuck in transition between a lymphocyte and the plasma cell. and they begin to have multiple genetic abnormalities that MYD88 mutation, the CXCR4 mutation and a variety of other mutations that I didn't mention often on chromosome 6.

So that can all point us to the fact that clearly the cells have made a genetic mistake and that has now caused them to grow faster than they should and have not allowed them to die like they should. So, we can tell when that's developed, we can tell that it's happening because of the genetic events but exactly why that happened is not well known.

And that feeds into the second part of the question and that is, is this something that is familial and there certainly are familial clusters. So, when one actually checks into family histories many times you will find that there are significant other numbers of people in the family that may have Waldenström's macroglobulinemia. That's not a given that it's true for every family but it's much more common than would be seen in other kinds of B cell malignancies.

I think the thing that's interesting about that is, is that because of genes that are being passed down through the family or is that due to the fact that there are common exposures to something that's triggering it. And at this point that's not well understood at all so a lot more research needs to be done in this area.

Lizette Figueroa-Rivera:

Thank you, doctor. And the next question is how do Waldenström macroglobulinemia and lymphoplasmacytic lymphoma differ or are they the same?

Dr. Stephen Ansell:

So, in essence, Waldenström macroglobulinemia and lymphoplasmacytic lymphoma are at their roots, the same thing. So lymphoplasmacytic lymphoma is what is happening in the bone marrow. In other words, when you look at the bone marrow under the microscope you can see lymphoplasmacytic lymphoma cells present however, to have Waldenström macroglobulinemia anemia you need the second part. You also need the high IgM levels and you can have some lymphoplasmacytic lymphoma patients that don't have any protein at all. Those would just be typically called lymphoplasmacytic lymphoma. When you can find the detectable IgM level that's what makes people Waldenström's macroglobulinemia.

Lizette Figueroa-Rivera:

Thank you. And I know that you touched on this during your presentation but there is a question, are there people who never need treatment after watch and wait and what percentage?

Dr. Stephen Ansell:

The answer to that is yes, there are people that have been observed with no treatment 30 years and beyond. Most of those people have the IgM MGUS meaning they have a monoclonal protein of uncertain significance. It could be detected in the blood, but it hasn't actually turned into anything specific. So that's why it's important to undergo a complete evaluation but it's also important to recognize that unless those additional symptoms are starting to kick in, one may not require treatment right away.

Lizette Figueroa-Rivera:

Thank you. And the next question, what should people look out for when on watch and wait for them to tell their doctors if things are happening that may indicate that it's time to talk about treatment? Are certain symptoms red flags?

Dr. Stephen Ansell:

So, I think this is a good partnership between the patient, the physician provider or nurse practitioner provider. On the one hand, the patient can be extremely helpful in alerting the doctor to when new symptoms show up. And as I highlighted the new symptoms we particularly want to know about are anything in the way of fevers or sweats or losing weight or difficulty with vision or difficulty with thinking or easy bleeding or any of those types of symptoms. Furthermore, patients may notice enlarging lymph nodes, may notice liver and spleen becoming bigger which might for example press on the stomach making it difficult to eat because you feel full very quickly. If new symptoms show up that should always be a red flag to tell your doctor about that.

On the doctor's side checking to see what's happening with some of the symptoms, with some of the lab values so things like what's happening with the hemoglobin, is the patient becoming anemic, what's happening with the platelets, are the platelets going down, what's happening with the protein, is that going up a lot and then there are additional blood tests such as the free light chain test or the beta-2 micro globulin test which are activity markers which give us a clue as to is there progress of the disease towards a more activated state.

So how the patient feels and how the blood test are trending together help to inform when is the best time to treat. I joke and tell people you want to be treated the day before you become too symptomatic. So, it's hard to know when that day is. You really want to be working with your doctor to get a sense of progression of the disease.

Lizette Figueroa-Rivera:

Sure.

Should people on watch and wait be careful about germs or to not get sick or is that not an issue during watch and wait, more so during treatment?

Dr. Stephen Ansell: So that's actually much more likely during treatment because treatment can decrease not only the monoclonal protein which obviously is the point of treatment but also good immunoglobulins, other antibodies making one a little more susceptible to infections. So, I think it's important to be careful about infections when you're on treatment.

For patients on watch and wait I think just good sensible behavior is good, regular hand washing, avoiding people that are clearly sick, but I don't think it's a substantial risk for patients and I think it's more important for folks to get out and enjoy the things they like to do and live a normal life. So, I would not recommend that they restrict their lives unduly.

Lizette Figueroa-Rivera:

Thank you. And the next question is, is it better to get a transplant earlier in treatment as part of initial treatment or first relapse rather than wait until a second or third relapse?

Dr. Stephen Ansell:

So, I think at this time because of the fact that there are so many new drugs that are highly effective in Waldenström macroglobulinemia, people are doing transplants later and later in the course of the disease. So, we tend to use it now as third and fourth line particularly in people that are very resistant and not benefiting much from previous treatments.

In the old days when we didn't have much in the way of good tools to treat Waldenström patients that made transplant much more useful, but we don't typically consider Waldenström as a first or even second line therapy, more typically we would use the chemotherapy plus rituximab or Ibrutinib approaches as our first lines of treatment.

Lizette Figueroa-Rivera:

Thank you. And the next question is my dad has very bad reactions to certain foods, is that related to the immune activity that's going on or is it completely unrelated?

Dr. Stephen Ansell:

I think that's a hard question to answer. What I mean by that is the actual protein, the IgM that's very high, is usually not specific for a food but is actually specific or sticking to proteins that are in a patient's body. And so, unless that very significant sensitivity to food correlates extremely highly with the disease coming on, I think that's hard to determine and I would be a little careful not to blame that on the Waldenström's.

Lizette Figueroa-Rivera:

Thank you. And I know that you alluded to this but at what point should a person receive the genetic test to see if they have the two mutations and is this necessary during watch and wait or wait until later?

Dr. Stephen Ansell:

So, I think there are two times when these tests are really helpful. Number one is when you're trying to make sure that the patient has Waldenström's macroglobulinemia and as I mentioned about 95% of people with Waldenström's will have this mutation so it's an additional piece of information that really confirms this.

The second part in the time that this would be useful is patients that are going to go on Ibrutinib, the BTK inhibitor. It seems as if those that have the mutation have a higher response rate than those that don't. That doesn't mean that you shouldn't receive Ibrutinib if you don't have the mutation but if you do, I think that increases your optimism for a good result.

Lizette Figueroa-Rivera:

Thank you. And while in remission should I be on some type of medication or will I be completely off any medications and free to live my life, travel, etc.?

Dr. Stephen Ansell:

So that depends a little bit on what the initial strategy of treatment was. Some doctors will be very much in favor of using a maintenance approach after chemotherapy. So, for example giving rituximab every two months and that is a reasonable strategy, those obviously that are taking Ibrutinib or other oral medications need to be on that full time.

Our strategy at Mayo Clinic is to consider if you do the chemotherapy is to do a defined period of time and then have patients off treatment. But all of these options are very successful and there's not one that's particularly better than another and that's something that I think should be discussed with your physician, nurse practitioner provider.

Lizette Figueroa-Rivera:

Thank you. And the next question is what are the typical late and long-term effects that I have to look out for?

Dr. Stephen Ansell:

Again, that's a great question and it depends on multiple things. Firstly, it depends on the chemotherapy that you've had. So, if you've had a lot of chemotherapy there are some long-term potential risk and those risks could be for damage to the bone marrow or other organs and so that's a reason to be in regular follow-up with your doctor.

A second thing that obviously is a concern is that because these cancer cells, the lymphoplasmacytic cells, are genetically unstable they may be able to what we call transform and actually become a more aggressive lymphoma and that can happen in about 20 odd percent of patients over the course of their lifetime. So, I think if ever a lymph node suddenly enlarges, or symptoms suddenly become much worse that's something that certainly should be alerted -- you should alert your doctor right away.

And then a further thing that is a risk is that sometimes with long-term treatment one's immunity becomes quite suppressed and when that's the case there is significant risk for infections. So often checking to see how the normal immunoglobulins are affected is important and it's important to keep up with vaccines and other things to remain in the best health possible.

Lizette Figueroa-Rivera:

Thank you. And the next question is, is there anything I can do involving nutrition that can help my immune system?

Dr. Stephen Ansell:

So that's a complicated question because as best we know there's not a specific food or supplement that could be taken that will directly improve the immune system against Waldenström macroglobulinemia. I do think however, the more you can do to keep your immune system in good health helps you fight off some of these infections and other complications that can develop and helps your body be in the best shape possible to tolerate treatment.

So, I encourage people to follow a healthy balanced diet, moderate exercise but there isn't a specific diet or supplement to the best of my knowledge that is going to entirely improve the patient's outcome and control the cancer directly.

Lizette Figueroa-Rivera:

Thank you. And what do you recommend to treat peripheral neuropathy?

Dr. Stephen Ansell:

That actually is a very difficult circumstance, and this is something that is best handled in conjunction with your doctor and a neurologist because there are two parts to that. The first part is obviously trying to get rid of the protein that is binding to the nerves and that's where in our practice, we often will use rituximab as treatment for that.

But the second part is there can be damage already done to the nerve and that actually is difficult to reverse and then medications to help with the symptoms may be the focus and that's where the neurologist can be extremely helpful in coming up with a medication regimen that will help with symptoms.

Lizette Figueroa-Rivera:

Thank you. And the next question is what is the role of radio immunotherapy in treating Waldenström's macroglobulinemia?

Dr. Stephen Ansell:

So, radio immunotherapy is where there is an amount of radiation on the back of an antibody that binds to the tumor cells and delivers the radiation directly to the tumor cell. That actually is something that has not been used much in Waldenström's macroglobulinemia and the reason is many patients with Waldenström's macroglobulinemia have a lot of bone marrow involvement. And one of the contraindications or reasons not to give radio immunotherapy to patients with lymphoma are those that have a lot of bone marrow involvement because the radiation will also hit normal bone marrow cells. So, in general Waldenström macroglobulinemia and radio immunotherapy we really haven't used it much at all.

Lizette Figueroa-Rivera:

Thank you. The next question is what are the chances the disease will come back more aggressively when you relapse?

Dr. Stephen Ansell:

So, there's not necessarily a direct correlation to the fact that if you've had it before, when it comes back it will automatically be more aggressive. The majority of time it comes back about the same as what it was before. In a rare patient as I mentioned before, you can get transformation where the cell genetically changes to a more aggressive lymphoma. That can happen. And when that happens then obviously the treatment and the management overall needs to change substantially. But I think as far as just the regular Waldenström's coming back, it comes back very similar to where it was in the first place.

Lizette Figueroa-Rivera:

Thank you. And our last question today is with all of the advances through clinical trials are there newer treatments less toxic than the older treatments?

Dr. Stephen Ansell:

Well, it's interesting because everything unfortunately has some degree of toxicity. The goal however is obviously to be as targeted as possible and limit the toxicities. Part of it also is how long you need to get treatment. So even though you may receive a more toxic treatment, if you receive it just for a very short period of time that may be very similar to having a less toxic treatment that you have to take for a very long period of time.


So, I think this is something that is best discussed with your doctor about what is really the ideal for you. Do you want something with more or less toxicity and what's the durability or the duration of the treatment that you're going to receive it? So, all of that I think are factors that will need to be discussed completely with your care team to make sure the best decision is made.

Lizette Figueroa-Rivera:

Well, thank you, doctor. That concludes the question and answer portion of our program. Dr. Ansell, thank you so much for sharing your time and knowledge with us today.

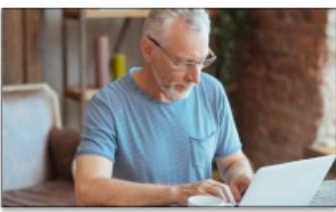

Dr. Stephen Ansell:

My pleasure.



The Leukemia & Lymphoma Society Offers:


- **Information Resource Center:** Information Specialists, who are master's level oncology professionals, are available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.
 - EMAIL: infocenter@LLS.org
 - TOLL-FREE PHONE: 1-800-955-4572
- **Free Education Booklets:**
 - www.LLS.org/booklets
- **Free Telephone/Web Programs:**
 - www.LLS.org/programs
- **Live, weekly Online Chats:**
 - www.LLS.org/chat




Slide 44 - The Leukemia & Lymphoma Society Offers

Lizette Figueroa-Rivera:

If you have additional questions please call a Leukemia & Lymphoma Society information specialist at 1-800-955-4572. Information specialists are available to speak with you from 9 AM to 9 PM Eastern time or you can reach us by email at infocenter@lls.org. We can provide information about treatment including clinical trials or answer other questions you may have about support, including questions about financial assistance for treatment. Also, please visit our online LLS community to connect with other Waldenström macroglobulinemia patients and caregivers at www.LLS.org/community.



- **Support Resources:** LLS Community, discussion boards, blogs, support groups, financial assistance and more: www.LLS.org/support
- **LLS Podcast, *The Bloodline with LLS*:** Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: www.LLS.org/thebloodline
- **Education Video:** Free education videos about survivorship, treatment, disease updates and other topics: www.LLS.org/educationvideos
- **Patti Robinson Kaufmann First Connection Program:** Peer-to-peer program that matches newly diagnosed patients and their families: www.LLS.org/firstconnection
- **Free Nutrition Consults:** Telephone and email consultations with a Registered Dietitian: www.LLS.org/nutrition
- **What to ask:** Questions to ask your treatment team: www.LLS.org/whattoask



Slide 45 - The Leukemia & Lymphoma Society Offers


LLS does have a Waldenström macroglobulinemia co-pay assistance program to assist patients with financial support toward the cost of insurance copayments and/or insurance premium costs for prescription drugs. To learn more about our co-pay program and see if funds are currently available, please visit www.LLS.org/co-pay.

Another helpful resource is the International Waldenström's macroglobulinemia Foundation, a patient founded, and patient led organization that supports everyone affected by Waldenström's macroglobulinemia while advancing the search for a cure. You may reach them at www.IWMF.com.



**THANK
YOU FOR
PARTICIPATING!**

**We have one goal:
A world without
blood cancers**



Slide 46 - The Leukemia & Lymphoma Society Offers

On behalf of the Leukemia & Lymphoma Society, thank you for listening and we wish you well.