

Diagnosis and Management of Waldenstrom's Macroglobulinemia

Waldenstrom's macroglobulinemia (WM) is a rare type of cancer that begins in the white blood cells. The abnormal white blood cells produce a protein that accumulates in the blood, impairs circulation and causes complications. It continues to be a clinical challenge for treating physicians as complete remissions and prevention of relapse are few in spite of all the therapeutic tools that are currently available. Besides treatment aspects, correct diagnosis of WM often poses a challenge.

We are talking to the Clinical Director at Bing Center for Waldenström Macroglobulinemia, Dr. Jorge J. Castillo about WM management touching upon diagnosis, when not to get treated, current clinical trials and more. Joining us bringing in the patient perspective is patient advocate and IWMF Trustee, Peter DeNardis.

Full Transcript:

Priya Menon: Hello and welcome to CureTalks. I'm Priya Menon, your host. Today's show is part of our Innovative Series where we discuss breakthrough treatments and research. We will continue our discussion on Waldenstrom's Macroglobulinemia. The focus of today's discussion is diagnosis, treatments and management of the condition. The featured guest on CureTalks today is Dr. Jorge J. Castillo, Clinical Director at Bing Center of Waldenstrom's Macroglobulinemia. He is a senior Physician and an Associate Professor of medicine at Harvard Medical School. Joining Dr. Castillo on the panel is Pete DeNardis, patient advocate and trustee of International Waldenstrom's Foundation. Welcome to CureTalks, everyone.

Dr. Jorge J. Castillo: Thank you.

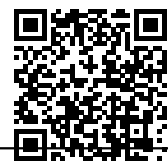
Pete DeNardis: Thank you.

Priya Menon: Dr. Castillo, as I understand it and I was just explaining to Pete here, Waldenstrom's is a tough condition to kind of completely understand. So, in layman's language, it's a rare type of cancer that begins in the white blood cells. The abnormal white blood cells produce a protein that accumulates in the blood, impair circulation and causes complications, right?

Dr. Jorge J. Castillo: Yeah, I think That is a very good way to put it. It is a type of blood cancer. This is specifically a type of blood cancer that falls within the category of a lymphoma and the malignant cells are lymphocytes that are typically nesting in the bone marrow of all of us. It's just that in patients with Waldenstrom's they have many more cells accumulating in their marrows. And one of the functions of these cells is to produce a protein called IGM, which is an antibody that is supposed to be protecting our bodies from infections, but in patients with this condition because they have too many of these cells, the levels of these IGM also increases, so patients tend to have anaemia, they tend to have an increased thickening of the blood because of the excess of IGM and sometimes the IGM can cause other problems too like nerve damage and increased size of lymph nodes in organs. There's a portion of patients who are asymptomatic as well. So, as you said it is interesting disease to take care of.

Priya Menon: And I believe it also continues to be a clinical challenge for physicians and so I want to start at the right at the beginning and start with diagnosis. What does the diagnosis process involve?

Dr. Jorge J. Castillo: That's a great point, most of the times to make a formal diagnosis of Waldenstrom's,



I think for me is very important because in my clinic this is what we see. So, I want to make sure that the patient sitting in front of me actually has this condition. So, I think the first factor that we almost always find almost always first, not always, but almost always is an increase in these level of IGM. There's actually a blood test and what happens sometimes patients have anaemia, sometimes patients have numbness in their feet, patients sometimes have just an abnormal value of a high protein level. So, there are many reasons why a physician will suspect something is not right with the patient. They might not be thinking about the Waldenstrom's precisely, but the number of tests they are going to be ordering can give us an idea that maybe this process is called Waldenstrom's. So, when we see a high protein or a little bit of anemia or some other problems, we tend to send in the blood is that test called electrophoresis of the blood, that really gives us a good idea of how the proteins in the blood are in that can gives us a sense that a protein is just maybe being over produced or over secreted. So, once we have an excess of IGM detected in the blood, which is a blood test first. The second day is almost always again, in some patients is not the same sequence, but in most patients, the next test will be to obtain a bone marrow biopsy. A bone marrow biopsy is a very relatively small surgery, almost never complicates, in which we take a piece of the bone from the pelvic area from a patient and the size of the bone marrow biopsy is very tiny, I don't know if you can see this, but it's something probably this size. Now, this is quite the size of the sample that we take. And we also take some fluid from the marrow and we send those for a multiplicity of tests that our pathologists are very familiar with to be able to identify what type of cell is the one that is accumulating abnormally in the samples and other features. We run genomic testing, mutation analysis and things of that nature. So, what we tend to see in that sample is usually an excess of lymphoma cells, in this lymphoma cells, have a very specific feature called lymphoplasmacytic cells. So, it is very specifically for Waldenstrom's. In any excess of these cells beyond what is expected is obviously another part of the diagnosis of patients with Waldenstrom's. More recently, I would say over the last 10 years, we have been able to refine that diagnosis by actually checking for the presence of mutations in these malignant cells and there is a specific gene called the MYD88. We all have that Gene but it's not mutated in us and hence is working well, but in patients with Waldenstrom's, they have a mutation in that gene and based on our experience more than 90% of the patients with Waldenstrom's can have a mutation in that Gene too. So when a patient comes to see me blood tests with an IGM elevation, the bone marrow biopsy, showing this excessive number of lymphoplasmacytic cells and the presence of a mutation, the MYD88 mutation, I think in that context with these three factors, I think the diagnosis of Waldenstrom's is very suspicious.

Priya Menon: So, once it is diagnosed, what is the next step like I'm trying to understand if monitoring Instead of intervention is an option at all, or what would be the most important factor which is considered for good prognosis. Because I was reading up that if you are diagnosed early age, age is a very important factor that is considered for a good prognosis. So, can you talk a little bit about that?

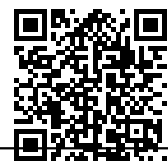
Dr. Jorge J. Castillo: Yeah, of course, I think that's a very important factor. So, in my clinic, for example, I would say, probably one out of three patients that I see for the first time in my clinic have the diagnosis, but they are asymptomatic. They have no symptoms from the disease. They don't have any anaemia, they don't have neuropathy, their IGM are high, but they don't have viscosity problems, they don't have enlarged lymph nodes or organs, they have no other manifestation of the disease, besides the fact that they have an IGM and the bone marrow is low. So, those patients we call them asymptomatic Waldenstrom's or some other people call it inactive smoldering. There are different ways of calling these patients. So, these patients are better left untreated and these are the patients that we tend to monitor without intervention and there are many reasons for that. So, as of today, we don't have a cure for Waldenstrom's, we're working on that very hard and obviously with the support of the IWMMF and other centres and research centres all over the world. We're all working towards a cure for this disease, but we don't have a cure as of today. So, when we think about that, we don't treat, then Waldenstrom's to cure, which is one of the reasons we treat patients with cancer. The other reason we treat patients with cancer is to prolong their survival and in patients Waldenstrom's from their survival has been increasing over time and over right now, many patients live for decades, so it is very unlikely that a six-month treatment or a year treatment or two-year treatment is going to change a 20-year survival. So, in most cases, when I say most, we don't prolong the survival of patients with Waldenstrom's, which is another common reason why we treat patients with cancer, right? either to cure or to prolong the survival. But in those two scenarios the treatment of patients with Waldenstrom's doesn't



really apply precisely. So, when do we need to treat patients with Waldenstrom's and the current approach is to treat patients who are symptomatic for one, we have to have symptoms that are severe enough to alter the patient's quality of life. And second, the symptom has to be related to the disease. So, there are two different factors that we need to have in mind because we can have patients who have symptoms from the disease, they're very minor and sometimes those patients might prefer not to get treated and that is okay. On the other hand, patient can have severe symptoms that might be the disease, but if you look a little deeper it is not the disease. So, it's better not to treat those patients because those symptoms are not going to get better with treatment, right? So, we need to be very careful about that. So, I think bottom line, if we have a patient with asymptomatic disease or minimally symptomatic disease, I think those patients are better left untreated. Those patients actually based on research from the Mayo Clinic, those patients who are asymptomatic and treated actually have a normal life expectancy. When you compare them with other individuals without Waldenstrom's of the same age, sex and race in this country, the life expectancy is normal. So, for all those reasons I think monitoring is a very important aspect of the care of patients with Waldenstrom's, specifically patients, who are asymptomatic. Now, most patients will need treatment at some point in their course of the disease, even the patients who are asymptomatic about 80 percent of those patients, will need treatment within 10 years and about two-thirds of the patients that come to my clinic, they already come symptomatic, so they need to be treated in those symptoms. As I said earlier, range from anaemia to neuropathy to viscosity to increase lymph nodes and things like that and at that moment is when we start thinking about treating. Now you ask me a question about prognosis and there are many ways of looking at prognosis. I would say the most important aspect in terms of prognosis is the age of the patient, patients who are younger tend to live longer and patients who are a bit older tend to shorter, that is life itself. We did a study some years ago in which we were separating the different causes of death in patients with Waldenstrom's and we realized the really the not Waldenstrom's causes were more prominent in patients with Waldenstrom's. So, most patients with Waldenstrom's do not die of Waldenstrom's, they die with it, they don't die off it. So, there are other causes that drives the survival of these patients, obviously I think age is an important marker of that a specific aspect. There are other values that we looked as well the IGM levels, the haemoglobin levels and things like that. I think an important aspect of all this is to how well the patient responds to treatment in that sometimes it's hard to predict, some patients will respond fantastically well and sometimes patients do not respond so well and again that is also something that we need to have in mind. But that is not something we can predict very early on by seeing the patient. I think it's more important to see the patient, follow the patients, see how the patients are doing and then we can get a better sense down the road how well the patient is going to do?

Priya Menon: You did mention mutations MYD88. And so, does these mutations where MYD88 or CXCR4 mutation affect your treatment decisions and you look for clinical trials for these patients because of what was the outcomes with standard therapies?

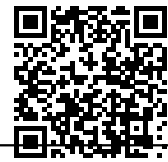
Dr. Jorge J. Castillo: Yeah, I mean you're speaking our language which is very nice. So, the whole genomic profile concept with the MYD88 mutations that we've seen over 90% of patients with a CXCR4 mutations, that we seen about a third of patients with Waldenstrom's and now the more recently, the TP53 mutation we have seen about 5 to 10% of the patients. There are specific genomic profiles that we can use to tailor treatment options. I don't want to say that those are the main drivers so far treatment options but they can definitely help us tailor treatment options. In patients with MYD88 disease only, for example, which is about half of the patients that have only the MYD88 mutation that's all they have. I mean, those patients tend to do relatively well, specifically with the newer treatments like oral agents that BTK inhibitors for example, they do very well with it. Patients with CXCR4 mutations are a little bit different. These patients tend to have higher IGM levels, they tend to have higher risk of hyperviscosity and have even more bleeding complications as well. They respond a little less well to the BTK inhibitors, they respond but they don't as good as patients without CXCR4 mutations. But in these patients chemotherapy, for example, works very well, proteasome inhibitors, which is another form of medications, tend to work very well as well. And then we have a very tiny group of patients without MYD88 or CXCR4 mutations, that's about 5 to 10% of the cases, those patients really respond even less well to BTK inhibitors and in those patients, we tend to use chemotherapy or proteasome inhibitors in that scenario. Now, there's another mutation, I mentioned the TP53 mutation that is a mutation that we have seen in many other blood cancers like, chronic lymphocytic



leukemia and other conditions- myeloma. So, Waldenstrom's patients also, some of them have these mutations too and basically, these mutations have been associated with chemotherapy resistance. So, these patients tend to not respond very well to chemotherapy. So, if a patient has this mutation we tend to use non chemo, treatments on those patients like BTK Inhibitors or BCL-2 antagonist or proteasome inhibitors. So as you can see we are studying to have genomic profile into account when we make treatment decisions in these patients.

Priya Menon: Dr. Castillo, what's on the horizon for treatment? Some novel therapies that will impact standard of care. Can you talk a little bit about that? And then maybe, talk about the recent CLOVER trial results, the targeted therapy for Waldenstrom's.

Dr. Jorge J. Castillo: Yeah. Of course, I mean, I think it's an exciting time for Waldenstrom's and we have an exciting time for the last 10 years. So, what I mean is, it's a momentum and I think it's, I think it's great to see that. So, as I said earlier, we have the standard treatments, right that most patients will be exposed, if they got to be treated today for example, we do have chemotherapies, we have proteasome inhibitors, we have antibodies, BTK Inhibitors, and BCL-2 antagonist, I mean that list has grown in my lifetime, which is an amazing thing to see. For the future, I think there are a number of treatments that are interesting, number one, we're starting to use combinations of these agents, we're starting to see what we call triplets which is essentially three agents at the same time and that has worked very well for CLL, that work very well for myeloma. So, I understand the interest of studying triplet therapy, triple therapy in patients with Waldenstrom's. Now these triplet therapies are going to include BTK inhibitors and one of the downsides of BTK Inhibitors, I would say, is the fact that they have to be taken indefinitely. So, these triplet therapies might actually explore the concept of using the power of using the BTK inhibitors without the need of having to take BTK inhibitors indefinitely. So, I think this new generation of clinical trials combining BTK Inhibitors with a finite duration of the therapy is actually a very important study and one of an examples is an Canadian study that is actually looking at Acalabrutinib, Bendamustine and Rituximab and Acalabrutinib will be in for about a year and then everybody will stop therapy. So, I think that's another very interesting study in that family of trials. The other trials that are of great importance are the ones that we call non-covalent BTK Inhibitors, these actually are third generation BTK Inhibitors and one of the other issues with the BTK inhibitors was the fact that they were associated with some bleeding issues, associated with cardiac problems like arrhythmias and things like that. So, there's a new new generation of BTK Inhibitors that actually might be effective even when the prior BTK inhibitors do not work anymore, and they seem to have also lower risk of bleeding and lower risk of arrhythmias. So, the two agents that are in development currently are Pirtobrutinib and Nemtabrutinib. And so, these are non-covalent BTK inhibitors, Waldenstrom's patients can be enrolled in these clinical trials, and I think those are very interesting, both of Agents. The other line of a branch of research where Waldenstrom's patients are getting into is actually immunotherapy and one of the agents of interest is the one, the CL131 from the Clover stud which I'll talk about in a second. We do have now antibody drug conjugates. There is a study with loncastuximab tesirine, which is approved for diffuse in large b-cell Lymphoma, it is an antibody drug conjugate targeting Cd19. It's already FDA approved for other conditions, so that's another study running. In very shortly, we will start with the CAR-T cell programs, for Waldenstrom's as well. There are a few CAR-T cell programs in the country that can enrol patients with Waldenstrom's but there's a program called Zuma 25 that is going to start actively involving specifically patients with Waldenstrom's and I think that's when I start later this year or very early next year, so we're very interested in that. There's another family of medications called BiTEs Bi-specific T-cell engagers and there's a number of them already being tested in CLL and in diffused large b-cell lymphoma and obviously want to be looking into those BiTEs for patients with Waldenstrom's as well. So, as you can see, very interesting time, in patients with Waldenstrom's will be many more treatment options. Now, the Clover study specifically, I think is of interest, number one, CLR 131 is a medication that was given at breakthrough designation by the FDA specifically to look at Waldenstrom's macroglobulinemia. They're looking at other conditions as well in the clinical trial. But one of the major focus is actually in patients with Waldenstrom's. So, this is an interesting mechanism of action because there's nothing that we have similar to that in anywhere else, which I think the impactful aspect of things. So, this is a Phospholipid Drug Conjugates or a PDC. And basically what they're doing is they're taking advantage of the fact that there are specific distribution of lipids in the membrane of the malignant cells specific in patients with Waldenstrom's



that is the difference compared to the normal cells. And in that way, it seemed to be targeting the malignant cells in a more specific manner than the normal cells in that specific situation. So, take advantage of that. They actually have a radioisotope associated with the drug. And in that way the radioisotope which is given intravenously, finds the malignant cells with that specific fat distribution in the cell membrane and then delivers the payload specific to malignant cells. There is already some data showing early efficacy. This was presented at one of the national meetings last year. There were small sample size about six patients but we've already seen some early efficacy with this agents. So I think it's going to be an important aspect of things. Number one, the mechanism of action is distinct. Number two, I think biologically speaking it makes sense. And number three is a finite duration of treatment. So, patient go in, they get just a few infusions separated over a couple of months and the patients are done. So, I think we need to, I will be very interested in seeing what the results so far of a study like this is going to be in the future.

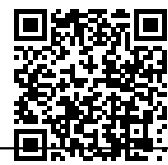
Priya Menon: What is the eligibility criteria for this trial?

Dr. Jorge J. Castillo: So, for this study patients need to have been previously exposed to other lines of therapy. So, this is not for a frontline treatment specifically and I think the ideal candidate would be a candidate who have already been exposed to the standard regimens, right? Rituximab containing regimen of some kind and a BTK inhibitor of some kind and probably in my opinion, that is where the unmet need is. And I think it's very interesting that this study is going to be able to target these population. This is second population that I think is of great importance is the population with this condition called Bing-Neel syndrome. Bing-Neel syndrome is a rare condition in which the Waldenstrom's cells gain access to the brain and the spine and causes neurological deficits there. That happens about one to two percent of patients, so it is not very common issue, but not too many drugs that we have available actually cross into the brain. The brain is protected, actually, very specific tissue is actually there's an actual physical protection. So, a lot of the treatments that we use for patients with Waldenstrom's that will go everywhere in your body will not penetrate into the brain. And therefore, will not treat Bing-Neel syndrome. So, currently for example, BTK Inhibitors cross the blood-brain barrier and some few chemotherapies that cross the blood-brain barrier in these medications CLR131 is one of those as well. So, a group of patients with Waldenstrom's in this study will probably have the Neel syndrome. And this is another population, that from my perspective, it's another big unmet need. And I think this study will potentially help develop treatment for these patients.

Priya Menon: Thank you. Thank you so much. Dr. Castillo. I have a few more questions, but I'm going to let Pete ask his before, being mindful of time here. So, Pete, all yours.

Pete DeNardis: Thanks Priya. And thanks, Dr. Castillo. Thanks to both of you for setting this up and having this presentation for the WM Community, I know as a WM patient myself. I really appreciate this and any knowledge we obtain is great knowledge to help us better manage our diseases. So, I guess one question I have is, I know Dr. Castillo you mentioned a lot of the newer BTK Inhibitors and the immunotherapy and the BITEs that are coming down the road. Do you foresee a time when that would be the standard for first line of therapy as opposed to Bendamustine and Rituxan or something along those lines?

Dr. Jorge J. Castillo: Yeah, I would say so I mean obviously I think it's a little challenging Waldenstrom's in the reason for that as you very well know, the ideal way to replace a standard of therapy is actually through a randomized study, in which you can actually show either benefit in terms of efficacy of safety. So, in the absence of randomized studies, is going to be very difficult to categorically replace one treatment option over another treatment option. But I do believe that the newer agents that are coming up are safe, are very effective and it provides patients with the difference approach to their disease. So, currently for example, I'm using a lot of BTK inhibitors in the front-line setting, for example, and I'm still using it. There are some patients in for I do recommends chemotherapy and other approaches like that. So, but I cannot tell you that there is one treatment that is the best treatment in the frontline treatment of patients with Waldenstrom's we did try to be more personalized. So, I think what we need is large, randomized studies to be able to show that that one specific treatment is superior to other treatments and that will be probably the best way to replace a standard of care.

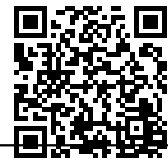


Pete DeNardis: Okay, thank you. And then as far as creating these large, randomized studies. What's the process? How do we help make that happen?

Dr. Jorge J. Castillo: Yeah, it is difficult because obviously it entails an expense, right? Sometimes either a pharmaceutical company or an academic organization is willing to take on. And number two, we need the compromise of multiple centers to run studies like that, we need multi-centre collaboration. So, we need to have the commitment and the compromise of a number of different centres willing to work together to be able to enroll patients in a specific study. So, in that sense, for example, the French and the Italians, and the Germans are really good at this. They put a National randomized study in every patient that goes into an academic center, will go into either center of care or the clinical trial, there is only one clinical trial available for everybody else. So, the enrolment in this type of situations is much more effective. In the United States, it's slightly more difficult. Number one because we're not working a lot together in Waldenstrom's specifically and number two is because there's so many clinical trial options, right? And so, when you go to a center or any center there are potentially competing studies running against each other for limited and small number of patients. So, that is potentially an issue. So, we are trying to set up a clinical trial network, a United States clinical trial network, and we are doing this in collaboration with the Mayo Clinic and other centers across the United States to try to at least start the idea of creating a clinical trial network. The clinical trial one of this nature actually existed in the past. And it was very, very effective. But with the new regulations and all that was a bit more difficult to sustain an effort like that. So, we need to kind of recreate that same idea for the new era so, we can actually enroll patients more rapidly and provide the best care to these patients as well.

Pete DeNardis: That's great. Thank you. Yeah, we'll be looking forward to that, for sure. Another question I have is you're mentioning the third line or third generation, the BTK Inhibitors that are coming along that have less harmful side effects. Can you speak a little more about like if someone is taking an alkylating agent, like bendamustine, what are the side effects he should look for and then on the flip side and BTK inhibitor, what should a patient be looking out for the communicate with your doctor that they're having problems in a certain area?

Dr. Jorge J. Castillo: Yeah. So, I mean, bendamustine or rituximab is one of the standard treatments for patients with Waldenstrom's. So, we were using this regimen for almost 10 to 15 years and has been extremely effective. The qualities I think of bendamustine, or rituximab is relatively easy to give, is two days every four weeks for six cycles maximum, and then you are done with therapy. This is an intravenous approach so you need to go to the infusion room to receive it and during the treatment patients are going to have decreased white blood cells, decreased platelets, decrease haemoglobin, constipation, rashes. So there's a lot of potential issues associated with the chemotherapy exposure and administration which a lot of doctors are very familiar with. I think one of the major concerns that I have personally, is the fact that there is a small risk of developing myeloid problems associated with the chemotherapy exposure. It is not very high, it's probably about a 1% or 2%, some people have challenged me on that whenever I say that, and they think it's actually a higher risk of having these myeloid neoplasms and this could be, myelodysplasia, it could be acute myeloid leukemia and these, myeloid neoplasms actually are not very easy to treat when the patient's, do develop these secondary to exposure to chemotherapy. So, I think in my opinion that is probably the largest issue from my perspective. And obviously, when I treat a patient who is 55 and that concern is difference when I treat a patient who is 75. So, we need to have these personalized discussions with patients. Now in the era of covid-19 infection and pandemic, the risk of infections is way much higher while patient is undergoing active chemotherapy and can be prolonged for 6 to 12 months beyond the completion of chemotherapy. So, some patients don't like the idea of being secluded to some degree protecting themselves and that would be another potential issue with treating patients with bendamustine or rituximab. Now, when we think about BTK Inhibitors is a very different way of treating patients with Waldenstrom's because patients take a few pills every day and that's all they have to do. There's no visits to the infusion room and things of that nature. These treatments are different in the sense that they are indefinite in duration. So, patients need to be taking these medications indefinitely so for as long as the medication is working and controlling the disease and there are not an acceptable side effects and the disease is not progressing, then the patients need to continue these treatments. And just to give an idea



about 20% of the patients, who studied the initial clinical trial in 2012, are still taking the medication today. So that's about a 20% rate of 10 years of longer duration of benefit. So, on one hand, I have a number of patients to tell well I'm already taking a bunch of pills every day, I don't mind taking in some more, and some are like I don't like the idea of taking a pill indefinitely. So, it has to do a lot with what the patient thinks might be the right thing for them. Now the side effects of BTK Inhibitors are very distinct. We do have I like to divide the side effects into different groups, the short term side effects and the long term side effects. The short term side effects, are the ones that the patient will have a little bit of diarrhea, bloating, maybe some reflux, some rashes, those are very easy things up to some degree to manage and most of them will actually get better over time, usually within 23 months of therapy all those symptoms tend to improve and the large majority of patients don't have to deal with those problems in the long term. Now in the long term, we do have other issues I mean bleeding is a big problem potentially in patients taking BTK inhibitors because these medications block how the platelets kind of stick together is very much like what aspirin does. So, patients can bleed with surgeries, patients can bleed more than the usual with trauma and things like that. So, this is not something that gets better over time. This is something actually sustains over time. So, patients need to be aware of this potential complication and obviously if they have a trauma, they're going to have a surgery, they to talk to the doctors. So, the medications need to be stopped sometimes for a few, for several days to try to minimize risk of bleeding. The other problem that we see over time is actually hypertension, actually that increases over time as well and we see that with Ibrutinib and Zanubrutinib as well. So, patients need to be aware of that and the issue is most of our patients are under the 60s and 70s, which is the age in which hypertension happens. So, it's very difficult to discern, if it's because of the BTK inhibitor or they were just having the hypertension regardless. So, we treat patients with hypertension normally as we would treat any other patient with hypertension and only the hypertension is hard to control, or the numbers are very high despite using one, two, three different medications at that moment, we can consider maybe decreasing the dose of these drugs. But we have not seen them very often. And I think the main concern, at the end of the day, it's just the arrhythmias- the irregular heartbeats that the patients can develop. The most common ones are atrial fibrillation, atrial flutter. This happens certainly more often with ibrutinib less often with Zanubrutinib. But they do occur with all the BTK Inhibitors even acalabrutinib as well. So, none of them are purely without these problems and patients need to know that if they have irregular heartbeats, if they're feeling their heart fluttering, if they're feeling that your heart skips a beat or any of these. They need to talk to their doctors so they can actually have a heart monitor placed and diagnose appropriately. Because if you leave an atrial fibrillation, untreated the risk of strokes go up really high over time so these patients need to have their heart rate controlled. They need to have their heart rhythms controlled sometimes and they need to be on a blood thinner in some scenarios as well to prevent the potential risk of strokes in the future. So again, the reason I focus so much on the toxicities, I mean, number one is the question that you asked my number two is because the efficacy of these two approaches bendamustine, rituximab and BTK inhibitors, the efficacy rates are pretty similar when we actually look at the depth of response, the time to the response, the durability of the response, all those numbers are almost superimposable in the absence of comparative trial. So let me be very clear about that there's no comparative studies but looking at the data and our experience it seems to me that both approaches are almost equally effective. So, we don't really talk too much about differences in efficacy, but rather the differences in how the medications are given, how long the medication is given, the side effects and all.

Pete DeNardis: Thank you. Yes, that's good to know as a patient who's on BTK inhibitor myself, I can attest to the fact that my medicine cabinet has gotten a lot larger now, do they have to keep other things under control, but I can't complain because the WM is in check. So, I'm happy with that. With these all these different treatments that are available and the novel agents coming along recently, have you seen that WM patients are living longer or that where that they also have a longer time period between needing to be retreated or I guess in the case of BTK Inhibitors needing to change treatments?

Dr. Jorge J. Castillo: Yeah, I mean obviously I don't think that has been formally evaluated in the most current era. I did a study using the epidemiological data base from the national cancer institutes, it's called the seer database. We publish this in 2015, 2016. So that was a while ago. And at that moment we actually did see that the average survival of patients with Waldenstrom's actually had prolonged over the last decade. So, I do believe that there is a benefit to patients. Obviously, we have no repeated analysis more



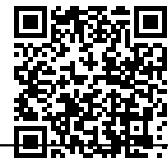
recently, I think probably somewhere around waiting a little longer to have a little more data to be able to run additional analysis with more recent data. So, I can't really give you a very solid answer and say that the patients are right now basically living longer. I think, yeah, I think in my sense is yes, I think the survival of patients has improved over time and probably will continue improving over time as well. But I don't know if it's because, we're better doctors or there are better treatments or there are just better patients. I think nowadays patients are very well informed of what is out there. They know a lot about the disease specifically, the population of patients with Waldenstrom's have the privilege to work with you and the IWMMF and basically see how well educated the patients are and how much on top of their disease they are and how much they understand the disease. So, I think that has a lot of value. I think a patient knowing their disease, understanding their disease, being an active participant on their own care, I think that actually is why these patients probably live longer. And obviously, I think our treatments help a little bit. I think the doctors help a little bit too, but I think the patient's knowledge and being an active participant in their own care. I think that's probably what's making one of the biggest differences here.

Pete DeNardis: Thank you. Yeah, I agree. Of course, you have to give credit also to the amazing clinicians and researchers like yourself that are out there every day trying to help patients and helping us on the path to living longer with the disease or in spite of the disease I should say. So, then you mentioned the immunotherapy, like CLR 131, then the Clover trial, how exactly does that work? I mean, our patients do we go into a radiation machine or is it a radioisotope that we take orally or what's the mechanism of that?

Dr. Jorge J. Castillo: Oh yeah. Those are the intravenous therapies. I mean, you don't need to go into a radiation area or anything like that, there should be some minor radiation precautions with the handling of the medication and things of that nature. And also when the patient received it, maybe afterwards a little bit, some minor precautions after that. We do have a lot of experience actually working with these radioisotopes. They were a number of medications approved, there are already a number of medications approved, different mechanism of action but also using radioisotopes for lymphomas in other cancers as well. So, the use of the isotopes is not new precisely but what is new I think is the fact that how they are taking advantage of the profile, of the membrane of the malignant cells to be able to deliver the real isotopes and stuff in a significant manner. But yeah, so it is that these are intravenous infusions. My understanding is there has been no infusion reactions in compared to what we see with antibodies and things like that. One of the concerns when we think about radioisotopes is, maybe prolonged cytopenias, when we have low hemoglobin, low platelets, low white blood cells because of the exposure, we have seen a little bit of that but it's not very prolonged. It seems to be reversible from the experience that we have so far reviewed. Obviously, what I think we need is more patient, right, to be able to see a larger number of patients, follow those patients for longer to be able to understand more about the efficacy and safety of these agent. But per se is a very interesting compound.

Pete DeNardis: Thank you. Yes. Thanks for clarifying that I was just wondering that the mechanism of that, but with regards to the novel treatments that are coming down the road, if you have a WM patient that comes to see would you say, hey, you should really go to this trial because I think it's amazing or there are a variety of options available to us?

Dr. Jorge J. Castillo: Yeah, so I mean, I tend to be a guide to the patients but the patient makes the decision at the end. So, I think there are a number of studies to be excited about and I think looking at what the patient feels maybe the right thing for them, I think is the most important aspect of things. So whenever I talk about a clinical trial for patients, so I talked about that non-covalent BTK inhibitor, somebody who's multiple relapse in that setting. So, we talked about ADCs, we talk about the CLR 131, we talk about the non-covalent BTK Inhibitors and basically what I do is I just go over what I think might be the case in each of those scenarios. A lot of have to do with how available and where these treatment these treatments are. Some patients may feel more appeal to go to the mayo and they have a specific study there while all the patient will be more comfortable going to New York City and there's another clinical trial available there. So I think it has to do with the design of the study, has to do with the mechanism of action, has to do with the geographical location of the of the clinical trial as well and in some cases even with our best efforts patients feel that a clinical trial is not right for them and they would like to try another standard of treatment again and



so we need to be able to guide our patients. I don't tell them what to do precisely but I review with them different aspects of the trials. In every trials with my patients, trials that we do at Dana Farber, trials outside of Dana Farber because by the end of the day we're looking for the best interest of the patients and if the best interest of the patient lies in a clinical trial in Tampa or Houston or Los Angeles and so be it. And I think that's the right thing to do.

Pete DeNardis: Great. Thank you. Yeah, I agree. I think any patients should have a good dialogue going with their clinician to discuss treatment options and sometimes I was always taken aback when a doctor says, well, the decision is yours, which one do you want? And it is a conversation. It's not a one size fits all kind of scenario, so I appreciate that.

Dr. Jorge J. Castillo: No, yeah, I agree and it's not a laundry list either like you close your eyes and pick one you want, right? It's not like that either. So, you need to talk about the pros and cons of each of them so you can make an informed decision. Now, the patient's decision, yes, has to be an informed decision so we have to provide that information so the patient can have all the tools they need to make decision.

Pete DeNardis: Thank you. Yeah, and one other question I have is probably not a fair question to ask of you but because I'm involved with the IWMF I get to see, or I stay on top of what treatments are approved or not approved in various countries and the novel agents have been game changers. And even the new immunotherapies probably coming down the pike will also be similar impact, but while they have less of a physical side effect, that's detrimental, they now have a financial toxicity aspect of it that we hadn't had to deal with before. Do you see that changing in the future for us? Like, are there any mechanisms in place that are going to make the costs more equitable let's say for patients and for me not fair to ask you but I'm just trying to advocate on behalf of patients that I have to contend with this.

Dr. Jorge J. Castillo: It's a question that we get asked all the time and I think the answer to that question is cost-effectiveness analysis which in the United States, we are not very good at that. Outside of United States, I think the UK is probably one of the best places to run a cost-effective analysis that actually makes sense. The downside of cost-effective analysis is that you have to put a price on a life. And that's why a lot of people don't like that approach right away wanting to put a price on a life. But that's how you measure cost effectiveness. And that's, I think a bit of the problem. Obviously, in the United States, at this time, we are in a system that is able to sustain this type of approaches without making a formal cost analysis, cost-effectiveness analysis. It might be that in the future, that might be something that we need to start doing. But again, I'm not even in health policy, so I cannot tell you exactly how this is going to work. There's a lot of issues with the Health Care system, not being able to negotiate the prices with pharmaceutical companies right, while this is done routinely outside of the United States. Just to give an idea the cost of ibrutinib outside of the United States is half of what The United States pays for that medication, probably this is this is common knowledge. So, I think that at some point if we get to a point in which the system is not sustainable I think, when I start looking into this type of cost-effectiveness analysis, at this time, at least United States, that doesn't seem to be too much of an issue, but I can foresee how these might be because they will be more and more agents coming out, approved costly ,indefinite duration of therapies. So maybe at some point this will become a problem that we need to look into, doesn't seem to be something that can be raised right this second, but it might be the case in the future.

Pete DeNardis: Thank you. Thank you. I don't think I have any other questions other than again, I just want to thank you, and thank Priya for setting this up.

Dr. Jorge J. Castillo: No problem.

Priya Menon: Dr. Castillo and Pete, I think that was a great discussion. Lot of information shared and it's time to wrap up today's session. So, thanks a lot for joining us on CureTalks today. Thank you both of you and this talk will be made available on curetalks.com. So, thank you, everyone and have a good day.

Thank you, Priya.



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