

Improvements in Myeloma Survival with Dr. Parameswaran Hari

You are 7 times more likely to survive three years in Dr. Hari's care than the care of an average facility that reports their data to the National cancer institute'. Discussing 'Improvements in Myeloma Survival' with clinical director of adult bone marrow transplant program and the associate professor of medicine of the division of hematology and oncology for the medical college of Wisconsin, Dr. Parameswaran Hari is editor of myelomasurvival.com Gary Petersen.

Full Transcript:

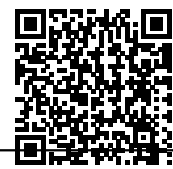
Priya : Good evening everyone. I am Priya Menon, Scientific media editor at Curetalk. On behalf of curetalk team, me Sharib Khan and Chintan Patel I welcome all of you to the myeloma cure panel here today. We will be moderating the call and bringing people live on the show. Cure talk launched cure panel last month, as series of monthly teleconference calls, where we brought together disease experts, patients, bloggers, family members and activists for discussion on latest treatments under development. Today's show is co-hosted by Gary Petersen of myelomasurvival.com. Hi Gary and welcome to the show. Gary needs absolutely no introduction. He is a 6 year survivor of multiple myeloma post his stem cell transplant. He works as myeloma specialist to provide life expectancy and survival statistics through his site myelomasurvival.com. His website objective is to help through the survival rate from 4-10 years. Our myeloma expert from the panel is Dr. Parmeswaran Hari from the medical college of Wisconsin. Dr. Hari Welcome to the curepanel. Before I hand over to Gary I would quickly go over some of the important rules, which will make the curepanel experience really smooth. If you are listening in to the panel as well as computer please mute online broadcast on your computer for better audio quality. All panelists are requested to stay within the time slot allotted. Callers have been invited to ask questions at the end of the discussion. They will let us know by pressing one the keypads. We will bring them on air live.

I think Dr. Hari has not called in yet. Dr. Hari if you are on air please press 1, we are not able to identify your number. Gary I think we can carry on with introducing the panelists. Gary will go on air now.

Gary : Ok What I would like to do is, would like to introduce the panel, in which we have 5 members, myself included, that are being treated by 5 different centers, with 3 very different treatment philosophies. However, we all have one thing in common and what that is that we all have a myeloma specialist on our team. And I think we are all pretty confident and believe that this is the most important element in achieving long term life expectancy. Our first panel member happens to be Matt Goldman and he is a myeloma patient with kidney involvement. He is a blogger and is being treated by an expert by name of Dr. Berenson of the institute for myeloma and bone cancer research – IMBCR. We have Pat Killingsworth who is a 5 year myeloma survivor and has just gone through relapse. So this is very very important to him. And he is undergoing treatment at Moffett. He has 2 blogs and I thought, it was 2 books, but apparently, while I was sleeping last night he wrote another one, so yes 3 books on myeloma. He is a dynamic advocate for the myeloma patient community. Not only that, the next month in October, he will be co-hosting, the next myeloma cure panel in October.

Now, the next blogger is Lora Polenta, and she is also a caregiver, and that is a difficult thing to do, because I know that now my wife had breast cancer and I became the caregiver from being the caretaker. And she is the caregiver her husband David who is a 4 year survivor and is being treated currently at the university of Arkansas Medical center in Little Rock, Arkansas – one of 2 locations where I received treatment as well.

Next is Keith Virgin. However, I think this is called advertising because, Keith is not a Virgin. Sorry Keith I could not help myself, but that is when it come to the disease. Because he has MGUS and that a precursor



to myeloma. However his disease has been moving towards smoldering and his fear of progression is very well founded. And that is because it is very unfortunate, because not only he and his father and his brother have had multiple myeloma. And his father and his brother have since passed. So, Keith is very concerned and understandably so. Keith is under clinical trial at the university of Arkansas for medical sciences.

Gary : Priya is Dr. Hari online?

Dr : Yes, I am online gary. thank you.

Gary : Ok. Dr. Hari I can only tell you how honored I am that you have given us the time to cover this topic, and also to Priya for giving us this forum from curetalk for doing this. Now Dr. Hari has many many achievements, the first of which is – he happens to be the clinical director of adult bone marrow transplant program and the associate professor of medicine of the division of hematology and oncology for the medical college of Wisconsin. Now that is quite a mouthful but it is not all that he has done. His myeloma program has the best 2 and 3 year myeloma survival rate yet presented on the myeloma survivor website, which means you are 7 times more likely to survive three years in his care than the care of an average facility that reports their data to the National cancer institute. He was boded to the national best doctors in 2011 and 2012, he is also the scientific director of the CIPMTR which is the center for international blood and marrow transplant research and this organization represents 500 transplant centers across the globe. I do however only have one issue with Dr. Hari. And that is that I struggle to pronounce his name. Dr. Rameshwaran Hari.

Dr : That is very good. Thank you.

Gary : Is that close Dr. Hari.

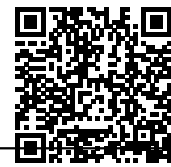
Dr : That is.

Gary : Ok. Our last doctor for the cure panel, by the way, needed only 7 letters for his entire name. And I got to say the next doctor is gonna be ad regime for my sake. But in any event, what I like to do now is, to start this presentation, if you don't mind.

Dr : Go Ahead Gary.

Gary : Ok I with start with, what I would like to do is, we will be talking about the disease progression in multiple myeloma, and that is something that all of the patients will one day be confronted with. And what I mean by that is that the disease will go through stages, first relapse, when it becomes refractory and finally we go on to a higher risk disease I believe. And as a result I was wondering if you might be able to give us a little background on these stages of the disease, and what types of treatment that you would recommend for this disease.

Dr Hari : Thank you Gary and Thank you Priya. I am also honored to be on this panel and help answer any questions that you may have. So, Gary's question really pertains to relapse. Now to call a situation relapse, by true scientific terms, the patient must have achieved a remission, complete remission prior to the relapse. So, if somebody gets to, what we call a complete remission, which essentially means that we did all the test that we currently have for myeloma and we could not find any disease, we call them in complete remission. And if from that point on if there is any recurrence of the disease, then it is called relapse. In multiple myeloma that term may not be the most accurate term. The better term is progression, meaning, your disease is beaten down but we know that in patients with myeloma, what determines a complete remission is our ability to detect disease. Even when we say someone is in complete remission, there may be small microscopic amounts of disease and that eventually leads to disease coming back or disease progressing from that point on. So, some people only achieve a partial remission to their initial treatment. Some people achieve what we currently call a complete remission thereby our current techniques cannot detect any disease in them. And in some cases we call a patient to be in stringent complete remission, which means that, even with some extra sensitive techniques we cannot detect disease. But eventually, the vast majority



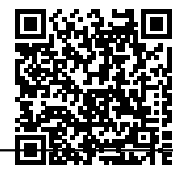
of patients do progress or relapse, which means the disease starts growing again and there is need for further treatment.

Now, to take issue with one that Gary said, it happens to all – it need not necessarily happen to all. There is probably 10-15% of people who have been treated in the last decade, who may not ever progress – meaning at 15 years they are still in their first remission, whether it is a complete remission or whether it is a near complete remission, you know, some sort of remissions, which does not get worse or does not progress beyond that. So that number, if we increase that number all the way up to 100%, obviously we have cured everybody. And increasing that number is the first step that we need to do. Because again as Gary suggested the best shot at treating myeloma is in the first go round, because the disease tends to be more sensitive to treatment initially, and when people relapse or progress, the disease becomes a little bit more complicated, more advanced, more resistant to drugs.

So, there is 2 things that we are dealing with here. One is how to prevent people from progressing or relapsing after their initial response and No 2 how to treat patients so that the treatment after relapse is also very good. So, there are twin issues really which will make long term survival measured in many decades, possible for the majority of patients. Now, that eventually, this is my feeling, will translate into cure. If we have a blast large number of patients not relapsing after their first remission, and even when in those people who do relapse, if we have effective treatments that can put them back into their original state. Those are the twin targets to get to a long term cure of myeloma. So let us address the first thing. So, the first thing is how to get to a deep remission which stays for a long time. Now when I talk to patients, one of the things that comes up – this question about – should I get to a complete remission – obviously, you know, having no disease is better than having some disease intuitively, but I would argue that time is what we have really, as human beings and as myeloma patients, or whatever we are, we look at it – time is really the one thing that we – the most valuable commodity. So, if you are in a complete remission and it is only a short lived one, it does not really mean much, compared to another person who achieves only a partial remission but, that is a long lived one.

So, disease control for a long time is the first goal of treatment. Disease control means non progressive disease – so the disease should not progress and it should stay like that for a long long time. So, currently we have very aggressive strategies that we employ in some people, like multidrug chemotherapy to achieve an induction response. So first drugs that we use, some people, some of the myeloma experts believe in using a combination of drugs that gets a quick deep response. And collection of stem cells and some, many experts believe in doing an upfront transplant which means – you do the transplant as part of the initial plan, irrespective of the response you got to the first round of treatment and then subsequent to that, what we call consolidation or maintenance treatment wherein, you do additional treatment in the form of chemotherapy to prevent the disease from coming back. So this is the most aggressive strategy that we employ right now.

Recently a study published by the CALGB group in the US, wherein patients who got initial treatment and an upfront transplant with their own stem cells, so an upfront autotransplant followed by the drug Lenalidomide or Revlimid on a low dose on an ongoing basis as maintenance. And that study approximately 50% of patients remained without progression of disease at 4 years. Now that is in a study setting, that is one of the best results we have. Now, the other argument that some myeloma experts also make is that you can also defer the transplant collect the stem cells and hold them in the freezer and continue with chemotherapy for a longer period and then, if and when the disease progresses from there, use the stem cells from that time. I personally don't subscribe too much to that philosophy unless there is an overriding reason not to do the transplant. Mainly because I think, the first remission – I am one of those people who believe that the first remission is the best remission, and in many diseases such as myeloma where, in many hematological diseases like myeloma, we find that the first remission is really always the longest. The second remission tends to be a little shorter, unless, we find a new drug which is blockbuster drug. So we have patients, when Revlimid was a new drug, their first treatment was not so good. We did not have such good treatments 12 years ago. They progressed and they got Revlimid on a study and then they are still going in their second remission – ongoing without a problem.



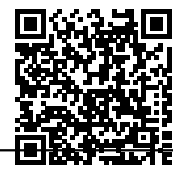
So unless we get a new blockbuster drugs, we have the same armamentarium that we have right now, we would expect the first remission to be the best remission. So, that is why I believe in a more aggressive approach. And right now the commonest aggressive approach is to do a 3 drug induction treatment. So when someone gets diagnosed with myeloma, they get a combination of 3 drugs. Usually in the US it is 60% of patients treated with those 3 drug combinations, with Bortezomib or Velcade, with Revlimid or Lenalidomide and Dexamethasone as steroids. So that is one combination. The second 3 drug combination is a combination of Bortezomib or Velcade with Cyclophosphamide or Cytoxan which can either be given as a pill or IV along with dexamethasone. So, the first one is called by RVD by some experts, or VRD – Velcade, Revlimid, Dexamethasone or Revlimid, Velcade, Dexamethasone and the second combination is CVD or Cyclophosphamide, Velcade, Dexamethasone. Or some people call it CyBorD because Velcade is also known as Bortezomib – CyBorD. These two combinations approximately are about 60% of all the new patients that get a transplant and then after 4-5 cycles of this, after response had been induced – the patients collect their stem cells and proceed to a transplant.

And then we have a national large study going where different forms of consolidation treatments or maintenance are compared. Now, that is the first strategy to prevent progression early on. So we try to get the first treatment to last a long long time. So, we say in the last decade 10-15% percent of patients are 15 years out without any progression, we are hoping that in this decade we can get, we can even double or triple that number to 40% of patients being progression free at NES for example.

Now that would be a significant achievement. We don't know that yet, but that is what we are hoping for. Now how do we know? So it is not feasible often to wait 10 -15 years to find out, and you know, what if it did not work. You know 15-10 year go by and we find that we are no better than we were last decade. So, we have some surrogate things which tell us that this might be actually happening. Now the commonest surrogate technique is, it is what we call defining Beep responses, now as I told you before, when we say someone is in a remission – we just say – we looked and we did not find it.

So, the second question becomes, how hard did you look? So, typically we look at things like M protein – which is a electrophoresis test that has been around since 1939. So, you can understand how long that is been going on. Then there is this test called serum free light chain, and there is of course this time tested bone marrow biopsy, where you get bone marrow biopsy and look at it under the microscope to count the plasma cells. So, this is the classic complete remission definition. but 5 years ago we defined a little more stringent definition – which is called a stringent complete response. Now the feeling or the early evidence is that if you look harder and you don't find any myeloma cells, that means that the patient is in a better state and that state is going to last longer, than a person who has detectable disease. And now a days, we have what we call multicolor flow cytometry – which is technique of counting 100's of 1000's of cell quickly from the bone marrow to see how many of these are bad plasma cells. Now there are also good plasma cells, you know, all of us have plasma cells which have an immune function in their body. So, if a person's bad plasma cells in a sample of 100's of 1000's of cells is minimal, then you are in a good better state. So, flow cytometrically defined remission tend to last longer. That we know. So what we are doing now, is in these aggressive strategies, we go back and look at people's bone marrows at light chain studies, and even there are molecular techniques of figuring out, how low you have gotten the myeloma down to. If by these newer modern techniques we don't find any myeloma cells in a person, or no evidence of myeloma cells – which means the biochemical tests are normal, the bone marrow tests are normal, even with the advanced techniques, that means we have less than one in million myeloma cells. If you get to that kind of a level, we believe it is going to translate into a longer remission. And that is really the goal of the people who pursue this aggressive strategy upfront.

Now to be fair, there is another group of people who believe that you don't really need to get those, because there is always a toxicity of treatment. If you increase the treatment intensity, you also cause toxicity. You cause side effects, sometime these side effects can be very severe and sometimes even fatal. So there is a counter-argument but, those doctors believe that even if you have a small amount of myeloma cells in your body, you can live with that for a long time as long as, you...and that is true. You know as Gary said in the initial introduction, there are people with MGUS or monoclonal gammopathy of unknown significance, who



are living with the myeloma clone, there is a little bit of early myeloma cell population in their bodies, but many of them, most of them actually don't even get to myeloma. So, the counter-argument has some merit to it. But in my view it does not apply to the vast majority of people. It applies to a minority of people where you can actually get the disease down and so, it all again boils to how aggressive is your initial disease. If you have an aggressive disease, it is unlikely that you can live with that little bit of that aggressive disease for a long time. You really have to get that disease down quickly and deeply and with as minimal trace of that disease as possible. Whereas if you have less aggressive disease, you could go back into a stage similar to MGUS or smoldering myeloma, and stay with small amount of paraprotein and small amount of myeloma cells in the body without them progressing.

So number 1 thing, the most important thing in a person who gets treated with myeloma upfront is control of disease – a long term disease control using either a way aggressive strategy or a less aggressive strategy wherein you preserve, you prevent side effects, but you got enough disease down, and the disease clone itself is not highly malignant or highly aggressive and the person can live with that for a long period. So that is number 1. Now the second part of your question, Gary, was treatment of relapse. Relapse is as again you suggested, it is near near universal but by no means universal. And the treatment of relapse depends on 2 or 3 things. Most important thing is how aggressive is the relapse. So if a relapse happens to a person we have treated aggressively and it happens, say, within the first year. It is unfortunate but does happen. That means it is probably a way aggressive clone that has come back, because it survived all this intense treatment – multiple drugs essentially combining most of the useful drugs in myeloma in the upfront setting, and then it comes back too quickly. So, in an early relapse, say after a transplant is bad. Secondly, a rapid relapse – meaning if someone's paraprotein say, is 0.5 today and 2 months later it is 2.5, it means that the myeloma cells are producing a lot of paraprotein in a very short time and the amount of myeloma in the person's body is exploding in fact. That is bad. Thirdly, some patients relapse with disease outside their bone marrow. We call that extramedullary relapse – which means the sites outside the bone marrow are involved in the myeloma. This can happen in the form of fluid collections around your lung, it can happen in the liver, and rarely, it can also involve this fluid around the brain, or the cerebrospinal fluid. All of these situations are bad and that again predicts for highly aggressive disease. So that is the aspect of the disease that affect how relapse is treated.

Secondly, it is aspects of the patients. This is how strong are you? So, it is always easier to pick up and treat disease in a person who is stronger. That is why we have the surveillance program. Most patients with myeloma who are on, who haven't undergone treatment come back and have their labs checked for myeloma protein, using free light chains or electrophoresis. Some people check it every 6 weeks, some check it every 8 weeks. Longest I have seen is people checking it about 12 weeks. So, somewhere between 6-12 weeks range, people are getting their relapse checked. And that needs to happen because, even before the patient becomes symptomatic or has symptoms of disease coming back, we need to detect it, so that we can intervene quickly, especially in cases of early relapse than aggressive relapse. Finally the important thing in how we treat this is what did you treat the person with upfront? So, if a person has been on Revlimid, for example, as a drug, and then they continue on Revlimid all the time, and say, 3 years later, the disease is progressing, they never got a transplant, their disease is progressing now while they are on Revlimid. So, at that time we would argue that the Revlimid is unlikely to be helpful and we would choose a strategy of a non-Revlimid containing regimen to treat that person's relapse. And then this person, specially who don't have a transplant, think about doing something like a transplant.

On the other hand if a person got a transplant and they had an early relapse – in the setting of transplant we define an early relapse as something that happens within 2 years of the transplant. If that happens it is less likely that a second transplant at that time is going to be much helpful. There are studies for patients with that kind of early relapse, where we do use a 2nd transplant, but then it has to be in some way different from the first time we did it. Either in terms of the specific drugs used, or maybe, it would be a donor transplant instead of a patient's own cells, or it might be in the form of maintenance after the second transplant. But again the point is that, how we treated the person in the first round, matters a great deal in picking drugs for the second round, when it does come back again. Another important thing is the type of side effects that the person got. Say, someone has physio-neuropathy on Bortezomib or Velcade. So this is one of the major side



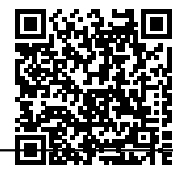
effects of Velcade, is the development of neuropathy, which is a nerve damage in the form of tingling, numbness, pain and difficulty walking, or using fine movements of the hands and that tends to happen to a percentage of people, that use Bortezomib. The numbers of people getting it have gone down in the recent couple of years because of changes we made in how we use the drug, but still it can be a problem. In such a person we have to be very careful about using that drug again. Now, we have alternatives, like, Carfilzomib and some of the the clinical trial drugs which don't seem to have neuropathy as a side effect, although they are in the same class as Velcade. So there are alternatives there. But, again, the point I am trying to make is that, the side effect profile from the first round of treatment is an important variable to consider, when we treat relapse.

Now let us see how aggressive you need to be with relapse. For a long time this was a matter of controversy and debate. So, say, someone has relapsed with their myeloma. We look at what agents they have been exposed to in the past, and we make a prediction of how each agent is likely to work. Suppose, someone had a transplant 5 years ago, they were not on maintenance and now the disease is coming back, and the only drug they got 5 years ago before transplant was say, Revlimid and Dexamethasone. Now you would expect in that person, pretty much any drug that we have right now. So, Revlimid would work because they had it for about 4-5 months before transplant. Transplant would work, because they had 5 years of remission from their first transplant. Bortezomib or Velcade would work because they have not even seen the drug. Conventional chemotherapy drug such as Cytosan or Doxorubicin would work because they have not seen that drug. Dexamethasone alone would work because they have only seen it for 4-5 months of Dexamethasone in the upfront setting. So, essentially in such a person have a wide choice of drugs they could go back to.

How do we use these drugs? So one group of doctors used to argue that you should use drug sequentially. So, in this person you would use Revlimid now and then keep going on Revlimid till the disease progresses on revlimid and at that time use Velcade. So that is the argument for the people who believe in sequential use of drug. So, you get maximum mileage out of each drug for the maximum period and then go on to the next drug. And then if couple drugs have failed then you try combinations so that is one approach. The other approach would be to use a newer 3 drug combination such as Bortezomib, Revlimid and Dexamethasone, which is considered an aggressive regimen as I alluded to earlier for induction. You use that to get a quick response and then do something in the form of maintenance of a second transplant or something. For the longest time, we did not have much evidences if one approach was better than the other. Then recently a paper was published in Journal of Clinical Oncology where investigator compared the use of Thalidomide and Dexamethasone with the combination of Velcade, Thalidomide and Dexamethasone. So 2 drugs vs. 3 drugs in the setting of relapse of myeloma- and that study showed that the persons who got a better 3 drug combination tended to have a longer time from progression of disease. So you get more mileage if you use a more potent synergistic combination of drugs. So, increasingly I am also convinced of that use, and in that scenario that I just described, where a person is essentially sensitive to all drugs that you have, I would treat them, if they were in good shape physically, I would give them a 4 drug combination and then even explore the possibility that they want to undergo a second transplant, and at that time use maintenance. We expect the second transplant to give people at least 50% or sometimes a little more than 50% of the time they got from the first one. So with this person I would go with Velcade, Revlimid and Dexamethasone combination for 4 months, and then do a second transplant and then put them on say, Revlimid maintenance. I would expect them at 3 years or so in that line, before their disease came back the third time. So this is one of the aggressive approaches at relapse.

The less aggressive approach as I told you earlier on, would be to use a single drug such as Revlimid and dexamethasone, get a response and keep going on that drug for as long as it is effective. So continued maintenance of that drug.

Gary : Ok. So the way I see it, your best shot is to take care of it, you know, the first shot is the best shot. Then what we have just heard from you is what you do at relapse, and you even talked about refractory meaning the disease does not respond to a certain drug like Revlimid and you would go on from there. You mind doctor if we go on from here with some of the questions from the other panelists.



Dr : Not at all. Please go on

Gary : Matt I know that you got to leave here relatively quickly, so would you ask Dr. Hari your question?

Matt : First of all doctor, thanks for your time. And I wanted to ask about patients that have either kidney involvement or bone involvement, when and if they relapse, does the disease manifest itself in the same way where you still just see kidney involvement or you still just see bone involvement.

Dr : So, That is a very good question Matt. So, the answer is that if you have a good doctor you should not see either of those involvements. So kidney involvement and bone involvement are what we call target organ damage in myeloma. So, the first time a person gets myeloma, obviously they were in good health, they never even have heard of this disease, suddenly one day they have bone pain or a back fracture or something like that and they get diagnosed with myeloma. And same thing with the kidneys, they go in feeling tired, they get anemic, not making urine and suddenly their creatinine is high, further work up leads to myeloma. Now, once person gets back in remission, the subsequent involvement with or relapse of myeloma, tends to, if we don't follow the person, and let thing happen, then you would expect the same thing to happen. So, kidney involvement typically with myeloma, is with the accumulation of light chains in the kidney and blockage of the tubules. That is what we call myeloma cast nephropathy. There is also other mechanisms such as light chain deposition disease, glomerulonephritis, urinary infection, many many ways in which myeloma related kidney damage can happen, but it all boils down to the fact that myeloma protein tends to get excreted through the kidney and it can block up the kidneys. The idea of being under surveillance as I told you before, people get surveilled or or people get labs done for the myeloma protein, between 6-12 weeks each time, every 6-8 weeks they are going to the doctor for having their labs checked.

Typically for people with kidney involvement it is light chains that are elevated, and if the light chains keep going up, we know the kidney damage is imminent and you need to intervene before that. So you would depend on your physicians to pick it up and intervene before the kidney damage sets in. So the second time around it is highly unlikely, if you have followed in any reasonable practice that you would end up in kidney damage again. That really should not happen. Same thing with bone involvement. If someone's protein levels are going up and they know that they have bone involvement in the first round, you would immediately try to intervene or, in the case of bone we have a test, such as the MRI or the PET scan in many instances where, early bone involvement can be picked up quickly and intervene. So, the myeloma protein happens to be a marker that gives us an idea that something is about to change, and then you need to intervene before tissue damage. In the relapse setting, intervention before tissue damage is possible and it should happen under the care of doctor that it really should be happening.

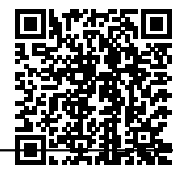
Matt : Ok. Thank you.

Gary : Ok Matt. Pat your question?

Pat : Doc can you hear me?

Dr. Hari : I can hear you Pat

Pat : Ok. I understand clinical trials are a wonderful thing and sure wish more patients would sign on. In most cases I know there is very low risk for the patient. For example, there was a Kyprolis study and the control group was using Revlimid and Dexamethasone and test group was using Kyprolis, Revlimid and Dexamethasone or something. Sure there is very little risk, but I am concerned about these, the push now for clinical trials for MGUS or smoldering myeloma, because, now you are exposing the myeloma to drugs earlier, and to me it is like starting of a meter in a taxi cab or something. Once exposed to the drug, it is like the meter starts. This is my impression. I am leading the list as I know, but I just wondered, how you feel about studies for treating smoldering myeloma aggressively early in an attempt to slow down the progression to symptomatic myeloma I guess. Do you have an opinion on this.

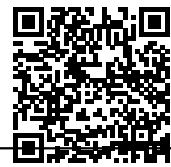


Dr. Hari : Absolutely. That is a very informed question and it is a tough question to answer. I was completely on your side of the equation on this question, till about 2 years ago. Let's put this thing in perspective, who may not be as informed as you are. So MGUS – monoclonal gammopathy of unknown significance and smoldering are what we call pre-myeloma conditions. The vast majority of people with MGUS actually do not go on to get myeloma. So, only about 20% of people convert to myeloma in their lifetimes. So if you get diagnosed with MGUS, odds are 80% chances that you will not even get myeloma in your life time. Smoldering myeloma on the other hand is a little bit more risky in that, 80% of people with smoldering myeloma eventually go on to myeloma, but 20% do not go to myeloma. So it is kind of the inverse here. Now in any clinical trial or any intervention medicine we really have to think of risk vs. benefit. In a person with MGUS, we have some risk stratifying tools which we use to assign a risk of, high risk of some people going to myeloma, vs. a lower risk in some other people. Even with these risk stratifying tools for MGUS, if the patients have been correctly diagnosed with MGUS, the maximum risk of transforming to myeloma is not more than 5-7% per year. So if you have 100 people with high risk MGUS, only a 5 or 7 people go on to myeloma.

So with regards to your question, to take an ongoing medicine, if it is a true medicine with side effects and all that kind of stuff, and get started on treatment for a situation where the overwhelming majority of people don't actually get into trouble, your risk benefit ratio I would argue is not in the favor of benefit. It is more in favor of risk, because you are taking an active medicine with side effects and that can cause trouble [00:40:37]. Whereas there are some trials in MGUS setting itself, with things like curcumin, or things which are really not medicine, diet modification, acupuncture, you know, things which have low risk of side effects and I would argue that those kind of things where the risk of side effects are low, it is reasonable to try them out. So, if it is an active medicine such as chemotherapy or Revlimid or medications which have a side effect profile that puts them in the strictly medication category. [00:41:06] You know if you change your diet and see what happens in MGUS, it would not be such a big deal, because the risk of changing diet is not so much and if there is a benefit, you would see it some people who have high risk of progression to myeloma.

In smoldering myeloma the situation is little bit more nuanced. Within smoldering myeloma as I told you, majority of people go on to have myeloma and actually, 50% of people go on to have myeloma within the first 5 years. So, we have again risk stratifying tools to identifying, who are these people who have a very high risk of progression to myeloma. In those people we call – high risk smoldering myeloma. It may be things like the amount of plasma cells in the bone marrow, if it is a high number of plasma cells in the bone marrow. It may be the proportion of good plasma cells to bad plasma cells in the bone marrow, that using a technique called flow cytometry. Actually the spanish group uses this as a primary criteria. It may be the ratio of light chains in your blood. If there is a very high light chain ratio, involving one of the light chain against the other one, that may be a high risk marker. So, patients with high risk smoldering myeloma have a much higher proportion of transforming the myeloma, even more than the 80% who go on to myeloma during the course of the next decade. So if you have a study for high risk myeloma, you could argue that you could have an intervention which makes a difference. Because the reason to have that argument is that, similar to the relapse situation where the myeloma becomes more difficult to treat at relapse, the argument is that maybe, smoldering myeloma is a pre-myeloma state, it might be easier to treat in the pre-myeloma state. So that is why there have been these trials. I was always torn whether to recommend that a person go on this trail or not. You know having seen myeloma day in and day out, you get a feel for this and when all the criteria point to a high risk smoldering myeloma patient, I now a days recommend a clinical trial to prevent progression to myeloma. In fact, there was a trial presented about 8-9 months ago at ASH from the Spanish where they put patients with high risk. They selected patients with smoldering myeloma of a high risk. So only the high risk smoldering myeloma, not all comers, received Lenalidomide or Revlimid and other group did not receive Lenalidomide. They were able to show that the people who did receive Lenalidomide had benefit in terms of survival. So there is at least one trial which was very nicely done, which shows that, you know, that trial has not yet been published to my knowledge. Until it is published it won't enter the full evidence base of medicine, but there are some signals that high risk smoldering myeloma population may be a population to target with an earlier intervention.

Now, you could also argue the other case. If you are targeting those patients with a low risk treatment, but if



you are 100% certain you are going to go on to myeloma, then why not give them a whole hog, treat them like myeloma. Now that may happen but, again, now you have argued both ways. You are introducing more risky treatment. So it is a very nuanced discussion. But I firmly believe that, you know the first question a person with smoldering myeloma or in MGUS situation has to ask their doctors – what is my true risk of progression track to myeloma. If that risk of progression is in single digits as it is for MGUS, it makes no sense to take a potentially harmful drug, a potentially harmful intervention, such as any drug that we use to treat active myeloma. Whereas, if that risk is high such as in high risk smoldering myeloma where there is risk of transforming to myeloma in the next 5 years, could be up to 90%, for the people with high risk smoldering myeloma, in that situation it may be reasonable to use the drug and get on treatment sooner. Because high risk smoldering myeloma may be easier to treat than active myeloma. There is this concept of additional mutations and additional genetic abnormalities that the cells pickup over time, and some of the second hits has not happened in many of these patients, and in that case earlier intervention might be more effective.

Pat : I understand the risk. I just think that say, if Lenalidomide, you now use Lenalidomide for 3-4 years, and the myeloma becomes active, it is unlikely that the drug will be very effective. Isn't it?

Dr. Hari : That is true. But the argument is that if you have high risk smoldering myeloma, you are not going to stay 3-4 years in that situation without needing some treatment. So the high risk smolderers definitely would not use for an MGUS and risk it. But if you have high risk smoldering myeloma the argument is that you are imminent myeloma, your myeloma is about to happen very soon.

Pat : It is still like, you know when I sat in, I think my first ASH 3 years ago where RVD was just starting to be used, I stood up and asked the question to the panel – wait a minute – aren't you exposing the patients to, you know, a second drug, and you know, it sounds like a similar argument.

Dr. Hari : Exactly. So that is exactly the point. So now we know that a better induction gives you a better response. So, and again Revlimid is the same thing after transplant. You are exposing patients to Lenalidomide maintenance and at a lower dose or all the same, but still many years of maintenance and then whatever comes back after that, maybe resistant, and the use of Revlimid after that is pretty much either going to be a short term or not effective at all.

Gary : Ok. We are gonna have to go on from here, if you don't mind.

Pat : Sorry Gary.

Gary : Sorry Pat. We are running a little bit behind. What we are gonna have to do is Lori and Keith, we are gonna have to cancel one of you two. Do I have anybody who can give up their time slot?

Lory : Go ahead Keith.

Gary : Thank you Lori I appreciate. Keith you wanna ask your question?

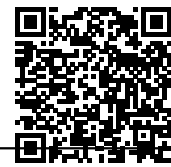
Keith : Dr.Hari. Can you hear me?

Dr. Hari : Yes I can.

Keith : Dr.Barlogie is working on the MGUS smoldering protocol at Little Rock, and I myself, I am taking curcumin and...

Gary : Keith. A feedback, do you have your computer on.

Keith : No. I am far away from it.



Gary : Ok. Alright.

Keith : Dr. Bargs got me on zometa infusion every 3 months And I am getting tested about every 2 months. My question is with the smoldering/MGUS, you know, I am wondering about the kappa lambda ratio. If that is out of sync, if that is a little bit high, going up, and your quantitative proteins are little high, and of course you heard about my background, is that a more likelihood that you will eventually develop myeloma, or am I just crossing the bridge before I get there?

Dr. Hari : [Audio failure]. then the chances of having myeloma are definitely higher than person who has MGUS. However there is a subpopulation of people with smoldering myeloma who never get to myeloma. The kappa lambda ratio being a little off, does not make much of a difference. For the kappa lambda ratio to be significantly considered a problem for smoldering myeloma, one of the light chains, either kappa should be 8 times or higher than the lambda or the lambda should be 8 times or higher than the kappa. So, I think I read your question of the email, and I think you said it was a kappa elevation of 2.5. And that is actually, you know, if it is a kappa smoldering myeloma, unless it is 8 or more, it really does not hit the threshold of being considered serious or high risk smoldering myeloma. So, a significant elevation in the number of plasma cells in the bone marrow, a significant elevation in the number of the kappa:lambda ratio 8 times or more, for one vs.the other, and there is a flow cytometric test where they look at the number of residual normal plasma cells in the bone marrow – So, if that number is less than 5% that again is a higher risk for transforming to high risk smoldering myeloma, so, based on your kappa:lambda number, it not all doom and gloom. And it is a matter of many things before it changes shape. If you have gone on for many years for smoldering myeloma, specially of you have gone on for beyond first five years from diagnosis with smoldering myeloma without getting to active myeloma, the risk of transformation actually goes down. So the highest risk of transforming from smoldering myeloma to myeloma is within the first 5 years after diagnosis. After that patients who have gone the first 5 years without transforming to myeloma, tend to transform more like an MGUS – a smaller number transform to myeloma each year.

Keith : Great doctor, my follow up to that, my M protein was 1.8 in the bone marrow, 1.8g/dl and the percentage of plasma cells was 12.5% in the bone marrow aspirate, and in the actual coarse marrow.

Dr. Hari : And how many years have you had smoldering myeloma for?

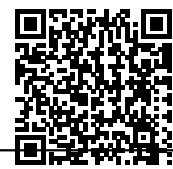
Keith : It will be a year in December.

Dr. Hari : So, based on the numbers you have given me, you do not fit the criteria for high risk smoldering myeloma, because I saw that your Kappa:lambda ratio was 2.5 or something, and 12% plasma cells and M protein of 1.8, you don't really fit the criteria for high risk smoldering myeloma. Your risk may be very low actually.

Keith : Well great. That is wonderful. I will pass it to Lori there, if Lori has questions.

Lori : My question was, you know, everything in myeloma was fluid and when I hear people talking with their local oncologist, as opposed to going to say, a research facility or even a specialist, there is a lot of talk about, you know high risk, low risk and then of course in Arkansas the ultra high risk – and the criteria being used for low and high risk in the local communities seems to still be far behind with what the researchers are classifying now as low and high risk. What as you understand it, what is the current criteria that you are using, or what are these changes as you understand them for determining a low risk or high risk patient?

Dr. Hari : So, for me the high risk low risk situation depends on randomized trials that we have done in the Europe and the US. Most of the factors are the well established ones. Cytogenetics, FISH based studies, and we use the plasma cell enriched FISH like most people do now, so that you find these abnormalities even in higher proportion of patients, and beta 2 microglobulin and the transfer stage. So, the large German multi-center study which was published in several papers over the last year, have shown that a combination of the international staging system and FISH defined abnormalities, for abnormalities such as 4:14



translocation or 14:20 translocation or chromosome amplification, or the 17p mutation are in combination with the international stage are really the most powerful predictors. So this is for patients undergoing aggressive strategies of induction followed by transplant followed by potential maintenance. So that is what we use in our standard population. [00:54:25] In studies, we use other markers such as Gene sequencing tests including the Arkansas model for gene expression profiling and other approaches that are being developed as we speak. So these are not well validated to it would be unfair to ask the community doctors to use them. So I think, a person with myeloma really has a right to expect, the community doctor stages them accurately at diagnosis and also orders plasma cell enriched FISH from their bone marrow. In fact, the difficulty in the community is that the first doctor that sees the patient and tests their bone marrow does not know that they have myeloma. When you go to myeloma center, that doctor already knows that you have myeloma and that bone marrow there will actually be tested for more things than the first bone marrow. [00:55:15] First bone marrow may be done for just anemia, or why is this person anemic, why is this person with a low white cell count? So that bone marrow is sometimes not sent for all the myeloma testing. And sometimes it is difficult to test it retrospectively. So, actually, when patients come to us and it haven't been done, we go ahead and do the testing again. So it is important to define both stage and cytogenetics at the beginning, so that you can classify patients accurately.

Dr. Hari : Sorry I could not hear your question?

Lori : I am sorry, some of the things that would classify someone as high risk, say 4 years ago are being very treatable now at some of the bigger facilities such as yours.

Dr. Hari : Right. Absolutely. So, but still you have to acknowledge that patients with high risk by the older definition, are now being treated with specific targeted agents such as proteasome inhibitors and proteasome inhibitors maintenance and combination treatments, which transform that risk. So, but unless you pick it up you won't give them those specific treatments. So It is important to still look at the same things that we looked at all these years, but now that we have treatments, you treatment is more targeted towards those risk factors. That is true.

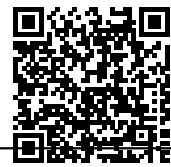
Priya : Thank you Dr. Hari. I think we need to open up the discussion for the listeners now. Listeners who would like to ask a question, please press 1 and we will bring you online to ask your question. Listeners who would like to ask a question, please press 1. Sarah you are live on air, please ask your question.

Sarah : My question is actually from a caregiver perspective. My boyfriend was recently diagnosed, he was 38 yrs old when diagnosed, he was in for surgery, he had a kidney removed and his levels were really off and that is when he was diagnosed with myeloma. He did treatment, he against his doctors wishes did not want to start with aggressive therapy. He went through Velcade and Dex and did not show any response to that. At this point I think he is tired and frustrated and kind of give thought to that he needs to treat this more aggressively, he had a lot of gum pain lately. Went to the doctor yesterday and learnt that he has a broken ankle. At that point they had decided to do additional blood reports and to have an MRI scheduled. I am actually going to the doctor with him on Thursday to see what we are gonna do next. This is the first appointment that I am going to with him, so, I am curious to know what I can expect and also what questions I should be asking at this appointment.

Dr. Hari : Thank you for the question. So looks like your boyfriend has fairly recently diagnosed myeloma that has not responded to a couple of cycles of Velcade. Is that right?

Sarah : Yes. correct.

Dr. Hari : He is exceptionally young for this disease. At age 38 he is about 3 decades younger than the average person with this disease. So, I concur with his doctor that his treatment needs to be aggressive, because he stands to loose more from this disease than many other people with this disease. Even with the best treatment, the chances of him making a long term disease control are not so great. Unless he really tries something extra ordinarily strong treatment. So, there is no reason to scrimp on the treatment now,



because as I suggested earlier, the first remission is really is the one that gives you the longest time, based on, provided no blockbuster drugs comes in the future. So and again, the way it get to those blockbuster drugs is to be around when they are in trials and when they are approved. So to get there we really have to get a good first remission going. So the first thing you need to ask your doctor is the extent of the disease, what is its international stage, where in he got this disease, why did the doctor recommend aggressive treatment upfront? was it based on his genetic markers of myeloma? What sort of genetic testing did he have for the myeloma cells to see, whether they were aggressive or less aggressive. So, those are the questions that define the prognosis of the disease in terms of cytogenetic markers and staging.

Secondly, you could ask the doctor, it would be unfair to get a day to day plan of what will happen next. But you should ask him, if taking away your boyfriend's wishes, what would the doctor wish the best treatment for his myeloma be. I know the name of your doctor from your email. He is one of the most respected myeloma doctors in the world, and I would absolutely ask his opinion, what would be the doctor's own plan for treatment, and then you should try to attempt of a conciliation if you will with your boyfriends concerns. Why does your boyfriend does not want aggressive treatment. What are his fears? Many a time when a patient decides he does not want treatment X or Y, and the doctor says, I think I should give you this treatment, it is not a completely irreconcilable situation. Your boyfriend may be worried about certain side effects, certain specific issues that he may want to be addressed, maybe worried about his work, maybe worried about the future in general terms, maybe worried that the treatment may end up causing more harm than good. So you could specifically address those concerns. I think you should have a talk to your boyfriend before you go and you should write down your questions. And basically your questions should be regarding prognosis, extent of disease, what he wants to do for the bones, what he thinks are the best treatment options from this point on. Velcade failure is not the end of the world and you should definitely give your boyfriend more hope. You know, in many ways there are much better drugs, much better combinations that we could have treated him with, specially if he has aggressive myeloma.

Priya : Dr. Hari, sorry to interrupt. We are running out of time. We have couple more callers online. Thank you so much. Brenda you may please ask your question, you have 30 seconds. Brenda you there?

[01:03:12] Brenda: Yeah. I am here. Thank for your time. Are you seeing any good data on any supplements that show to be helpful with multiple myeloma?

Dr. Hari : Not in our sort of literature. However, there is this feeling that curcumin which is a supplement, it is something which is used in cooking in many parts of the world, has anti-myeloma activity. Turns out that it is not an easily druggable compound. People are working on it trying to make it a drug. But curcumin does work on the NF kappa B pathway which is important for survival of plasma cells. And that is one of the most well validated supplements. But in general not much in terms of supplements that works as well as some of the drugs we have.

Brenda : Thank you.

Priya : Thank you Dr.Hari. Patricia, please ask your question

Patricia : Thank you. I am 64 year old Multiple myeloma patient at the Sidney Kimmel Cancer Unit at the John Hopkins hospital in Baltimore Maryland. I am in partial remission. I completed a drug therapy in June. They wanted me to do a stem cell transplant, which I did not want to do, so they recommend me a clinical trial, which I am in and chose to do, which is the Armatostat-GRN163L and I am doing pretty good there. I just want to know, what your prognosis is of that study.

Dr. Hari : That is a very tough question. I guess you reserved the toughest question to the end. Because it is a study, because we don't really know. I didn't catch the name of the drugs. What are the drugs that you are receiving now on the study?

Patricia : It is Armatostat-GRN163L and Imetel..



Dr. Hari : Ok, Imetelstat. I do know about this drug a little bit. So, that is actually a very reasonable study to attempt. However it is as far as I know a phase 2 study, which means that we don't really know if it is better than anything else we have in myeloma right now. So, it is an early phase study. Based on how this drug works, and based on the laboratory experience with this, it is a very new type of treating myeloma, in that it blocks a specific RNA pathway on the myeloma cells and we should expect it to give you benefit from that. Specially, if you did not want to do the transplant at that time, this is a very reasonable approach to try out. I am hoping that you have your stem cells collected and stored. Right?

Patricia : No. Did not do that either.

Dr. Hari : You did not do that either. I would probably that be the only thing, you know, at your age you are young. You should think about having it as a backup, having that in the back pocket, even if you choose not to have it now, you may want to have it done later at some other point. So you may want to discuss that with your doctor, regarding having them collected and stored in the freezer, so that you may use it later if you need it.

Patricia : Ok, Thank you very much.

Priya : Thank you very much Dr. Hari. Gary, I think we can summarize the discussion for now please.

Gary : Ok, so is that the end of the discussion then?

Priya : Yes, you can summarize the discussion Gary.

Gary : Dr. Hari, thank you so much for agreeing to do this in the first place and for your expert advice and counsel. And I think that we all appreciate what you have done. You are obviously quite skilled and I think all people should have skilled professionals on their team. And the one thing that you said that the best treatment for the relapse just happens to be never to have a relapse. So, that and your methods by which you would be able to do that. And, so, I think that, if any thing that came through loud and clear, and I can't tell you how appreciative we are of your efforts and your help with this call. I apologise of I at all interrupted, I was just trying to keep the process going through, because we know that we had a number of people at the very end who had important questions that we needed to get, so thank you for your presence.

Dr.Hari : Thank you Gary. Thank you so much. I really appreciate the opportunity to be on this panel and thank you for keeping me on time. Actually I appreciate you doing it.

Gary : You were wonderful.

Priya : Thank you so much. It was very great to hear such a lot of information on the panel today. Dr. Hari it was great to have you on our panel. Thank you so much for taking out time for this venture. Many thanks to our panelists Pat, Matt, Lori and Keith for making this panel discussion flushed with the patient perspective. Curetalk thanks all participants and listeners who extended their support of for the panel today. Special thanks to our co-host Gary Petersen, who was the driving force behind the myeloma panel. Thank you Gary.

Curetalk will be conducting monthly myeloma curepanel and encouraging patients and bloggers to come forward and to cohost the show with us. This is a new venture initiated and hence we need support. Please let us know your feedback. Drop me a line at Priya@trialx.com

Thank you so much everyone. It was lovely having you all here. Thank you.

Bye.