



Total Therapy and Myeloma with UAMS

Total Therapy is the only program in the world which talk about a cure for myeloma. Total Therapy is based on the approach that the best chance of eliminating all disease is at the beginning of treatment when the cancer has not been exposed to any drug and has not developed any resistance. As Gary Petersen mentions on his website, myelomasurvival.com, the most recent data on Total Therapy shows average life expectancy of 15 years for their TT3 program and this is 3.8 times longer than average of all facilities that report their survival to the National Cancer Institute. To learn more about Total Therapy, stay tuned.

Full Transcript:

Priya Menon : Hello, everyone, and welcome to the Cure Panel Talk Show on myeloma. I am Priya Menon, Scientific Media Editor at Cure Talk, Cure Panel, joining you from India and I welcome all of you this evening to a discussion on multiple myeloma. This is our final show for the year 2013 and we have conducted over 20 shows on myeloma and these have been heard over 30,000 times by listeners. We have been fortunate enough to feature eminent myeloma experts including Dr. Pal Richardson, Dr. Robert Orlowski, Dr. Shaji Kumar on the show; and we have been overwhelmed with the support that we have received from our panelists, Gary Petersen, Pat Killingsworth, Jack Aiello, Nick van Dyk, Cynthia Chmielewski, Lizzy Smith, and our participants and supporters who have been with us through this myeloma journey. We have quite a few interesting shows lined up for you in the coming new year too and hope we enjoy your support to bring you the latest in the field of myeloma research. All details of our upcoming shows can now be accessed at curepanel.carefeed.nic or you can always mail me, priya@trialx.com.

Today 's is the 40th episode of the Cure Panel Talk Show. Our previous episode on myeloma had Dr. Asher Chanan-Khan of Mayo Clinic discuss monoclonal antibody therapy in myeloma. Today, we have a very distinguished myeloma expert joining us. My co-host for the evening is myeloma survivor and editor of myelomasurvival.com, Gary Petersen. Supporting Gary on the panel are myeloma survivors and advocates, Pat Killingsworth, Jack Aiello, Nick van Dyk, and Cynthia Chmielewski.

Today, we are discussing Total Therapy for myeloma. Total Therapy is the only program in the world which seems to talk about a cure for myeloma. Total Therapy is based on the approach that the best chance of eliminating all disease is at the beginning of treatment when the cancer has not been exposed to any drug and has not developed any resistance. As Gary Petersen mentions on his website, myelomasurvival.com, the most recent data on Total Therapy shows average life expectancy of 15 years for their TT3 program and this is 3.8 times longer than average of all facilities that report their survival to the National Cancer Institute. To learn more about Total Therapy, stay tuned. I will now hand over to Gary Petersen who will introduce us to the expert and begin with the show. Gary, you are live.

Gary Petersen : Yes. What I love to do right now is to introduce everybody to Dr. Frits van Rhee. He is internationally known multiple myeloma researcher and a Professor of Medicine at the University of Arkansas Medical Sciences College of Medicine and he is also the Director of Developmental and Translational Medicine in the Myeloma Institute. He became the inaugural recipient of the Charles & Clydene Scharlau Chair for Hematological Malignancies and Research and this particular chair had been funded with a million dollar donation from one of the people being treated at UAMS. He joined the Myeloma Institute in 2001, establishing a laboratory for developing innovative medical treatments using the body's immune system. He is a leader of multiple National Cancer Institute-funded grant programs and projects related to the developmental therapeutics and anti-myeloma effect of natural killer cells in the body's immune system. He has an exceptional background, earning his degree in medicine in the Netherlands, then continued education at the University Hospital at Oxford and also at the College of Science, Medicine, and Technology at the University of London and finishing it off before going to UAMS at our own National Institute of Health here in



the United States. So, doctor, exceptional background you have! In addition, you are one of the key experts in all of Castleman's disease and those two other people who get that every year, I am sure I am very happy to have you in their corner given what I have read about some of the wonderful things you have done for people with that disease. So, doctor, welcome to our program!

Dr. Frits van Rhee : Thank you for having me and thank you for the wonderful introduction and I will try to keep up to it.

Gary Petersen : I think you will, without doubt. First, I would like to ask a few questions and I had several, but I think I am going to little it down to just three for the introduction because the panel has introduced so many great questions that we will get to them with their questions a little bit quicker and so, Dr. van Rhee, would you provide us a little background on UAMS Multiple Myeloma Program and in this concept of Total Therapy?

Dr. Frits van Rhee : The myeloma program here was started by Dr. Barlogie in 1989. He came originally from Germany and worked with MD Anderson and started treating myeloma patients here in the Arkansas. He uses a concept which is called Total Therapy which applies all available drugs upfront in combination with stem cell transplantation. Development of Total Therapy is based on the concepts which the St. Jude's Children's Hospital has developed for the treatment of acute childhood lymphoblastic leukemia. Here, they used induction chemotherapy to get the disease under control. Later consolidation was added and then maintenance. We used similar concept in the care for myeloma. This is in addition of stem cell transplantation. And now from this stem cell transplant is a way of getting the patient into complete remission. It is estimated that the single transplants will induce complete remission rate of 20%. Most of them do two transplants in multiple myeloma. It was again modeled on acute childhood lymphoblastic leukemia where cures were seen when the CR rate, the complete remission rate, was 40%. So, the idea was if we do two transplants in a row, we get 40% of patients in remission and perhaps we are going to see some cures. So, that's where the concept of tandem transplantation comes from and again there is upfront induction chemotherapy when in analogy to childhood acute lymphoblastic leukemia, there is consolidation dose to reduce the chemotherapy _____ and again there is a maintenance phase to suppress and eradicate any residual disease. Over the years, we gradually introduced new drugs including thalidomide, later bortezomib and also lenalidomide.

The other aspect, I think, which is unique of the Total Therapy concept under the Arkansas program, that we do try to follow patients very long term. So, we have a unique long-term followup. We like to think that we provide care from the cradle to the grave, so to speak, and we have been following our patients in the comprehensive fashion, introducing cytogenetic testing at the onset of the program, MRI shortly thereafter. We introduced gene expression profiling on all patients in the year 2000 and shortly thereafter assessment by PET scanning as well. So, these are sort of the unique features of Total Therapy and the program.

Gary Petersen : You said gene expression profiling, how does your treatment, how is it impacted by gene expression profiling?

Dr. Frits van Rhee : Dr. Shaughnessy used to work at our institute, developed a gene expression score based on the expression of 70 genes which were either over expressed or under expressed in myeloma and separated the patients into two groups – a diagnosis 85% of patients have standard or low-risk disease and 15% have high-risk disease. We have found that with the Total Therapy 3 program, we made substantial progress with the introduction of bortezomib in the standard or low-risk group but not in the high-risk group. The high-risk group is characterized by an increased propensity to relapse. In other words, patients will go into remission with equal ease but has a higher relapse rate than standard or low-risk patients. So, based on the observation that in the Total Therapy 3 program, patients with high-risk fared significantly worse, we developed two different treatment programs – one is called Total Therapy 4 standard or low risk, which was essentially based on our prior Total Therapy 3 approach and different approach, a different protocol for patients with high-risk disease. In other words, the gene expression profile score being high or low risk assigns patients to a different treatment program.



Gary Petersen : I see... Very good! One thing, I am sure you are aware of, is that your program does have some of the very best survival statistics in the country; however, it also seems to be under fire sometimes for being too aggressive and sometimes the quality or the integrity of the data is often questioned and I believe most of your survival data comes from clinical trials and it was my understanding that clinical trials and the data from the clinical trials are audited by outside firms to ensure accuracy, so can you comment on that and give us your perspective?

Dr. Frits van Rhee : Certainly. There is in the myeloma community debate treating patients to control the disease versus cure. In my view, both approaches are not mutually exclusive. I think it would be unreasonable to give a 78-year-old person highly aggressive therapy and that it would be very reasonable to control the disease. On the other hand, in younger patients, they really want to have long-term outcome. More aggressive therapy can induce long-term remissions that are potentially true of the disease and that's where you would treat more aggressively in my view. With regards to the integrity of the data, I believe that we are the only program who actually audits our own data. We have an independent auditor, auditing team coming in two or three times a year and they have audited us 25 times since 2005, starting with our Total Therapy 2 program, 78% of the patients in Total Therapy 2 were audited, about 90% of patients in Total Therapy 3, and in the order of 55% of 60% of patients in Total Therapy 4 and 5 have been audited. In addition to that, we have had FDA audit in 2004, 2008, and 2012. We also have an internal compliance office at our institute which audits as well. So, these data are truly very rigorously scrutinized.

Gary Petersen : Well, thank you, and one last question from me and then I will open it up to the panel. The evolution of the TT program seems to add new drugs, yet the intensity of the treatment has been reduced, meaning that I think there is one induction now in TT4 and one consolidation and also the Melflam is now reduced dosing by three times or something similar to that and even though the intensity has reduced, these new drugs apparently have significantly improved survival. As a matter of fact, I did little data mining myself and according to TT1, the six-year survival is 50%; TT2 without thalidomide it was 58%; TT2 with thalidomide, so you have an IMiD at 62%; and then TT3 which included bortezomib, protease inhibitor, was 70%. So, you are 1.7 times more likely to survive if you had TT3 than if you had TT1, so I think that's quite significant and that leads me to the question. What do you see as the next steps in the progression of the TT program, carfilzomib, pomalidomide, monoclonal antibodies, or vaccines, where are you going with your next step and what is that next step that you see?

Dr. Frits van Rhee : So, confining ourselves to the high-risk patients, I think we have developed a different protocol which is called Total Therapy 5 for high-risk patients which is little bit modeled on how some German groups have treated very aggressive lymphoma, which is usually treated with a combination chemotherapy called R-CHOP and they apply that chemotherapy more frequently. So, what we have done in Total Therapy 5, we treat patients at six-weekly intervals with combinations of drugs. In other words, we reduced the treatment-free periods, but we de-escalate the dose. In other words, the patients get more frequent therapy, but the doses are less. The idea is that during the treatment-free periods, there is no regrowth occurring of the myeloma. In other words, we keep tumor kill ongoing and we have observed that with that approach patients go quicker through the treatment program. Up until the maintenance phase, they do better but relapses occur during the maintenance phase.

When we look at our Total Therapy 5 program in which we used what we call a dose dense that is giving the chemotherapy closer together approach we found that the overall survival was bettered and we think that the overall survival was bettered due to the appearance of new drugs on the market. In other words, the survival is better because some patients relapse. They have better salvage and the drugs that we use particularly in that period of time is carfilzomib. We have now new version of Total Therapy for Total Therapy 5 which is hopefully going to be activated within the next three to four weeks in which we are going to use carfilzomib instead of bortezomib during treatment for high-risk patients. Substitution of bortezomib for carfilzomib, we hope, may improve the outcome in the high-risk setting. I think in the patients with low risk with these, we need to try and figure out exactly who benefits from what. We have been criticized for being too aggressive. Our maintenance is for three years with bortezomib, Revlimid, and dexamethasone – some people comment that we don't use maintenance with extended treatment for three years, then the question arises of who



exactly needs which drugs. We have some clues, who may benefit from certain drugs. Total Therapy 2, we did not have bortezomib available. We found certain molecular subgroups which clearly benefited lots from the introduction of bortezomib. These are patients with the 4;14 translocation, patients with deletion of p53, patients with high predictable _____ cytogenetics. So, we are able to see patients who benefit from proteasome inhibition and perhaps you can also see that other patients who perhaps have more genomically stable disease _____ Velcade and perhaps could benefit from a more immunomodulatory approach that will be combination of immunomodulatory drug for instance with a monoclonal antibody and the two would work synergistically or a combination of immunomodulatory drug with a vaccine. So, those are thoughts we have currently on how to develop the approach for the standard or low-risk group.

Gary Petersen : Well, thank you so much, doctor. You have done an excellent job explaining the program and I think I would like to ask some of the people on our panel to ask their questions. Nick van Dyk, your's, first question and only one question at a time.

Nick van Dyk : Perfect. I am here. Can you hear me?

Dr. Frits van Rhee : Yes, very well.

Nick van Dyk : Excellent. So, first of all, hello Dr. van Rhee. My questions tend to be long and today is unfortunately going to be no different. As many listeners are likely aware, I am a patient and dare I say, even a friend of Dr. Barlogie's and I am a pretty fierce component of your work, so first of all, I want to thank you and your colleagues for saving my life. I was diagnosed five years ago at the age of 40, so I was definitely in the young-and-want-to-get-rid-of-it type of the code word. Having said that, we sometimes get the toughest questions from the ones you love and so this is going to be a tough question. Total Therapy, as you mentioned, from its first trial looked to stuff like pediatrics, ALL, where you observe a plateau of remission log _____. In other words, after some period of time in remission, the likelihood of losing it goes to nearly zero and on that basis you sought _____ excessive plateaus in Total Therapy 1, it may be 15 or 20 years out; in Total Therapy 2, much closer and initially I read a presentation published a few years ago called The Myth of Incurability that suggested the plateau for Total Therapy 3 would be around six years out. In other words, if you lasted six years, you could be relatively certain that the disease wouldn't be coming back and then this further got updated in a presentation called Modelling for the Cure in 2009 that showed an extraordinary number. If you are a low-risk patient which is about 80% of patients and you achieve complete remission which was about two-thirds of those people, that 90% of that group could expect to be cured. However, neither these presentations are found on the website any longer and I know that Dr. Barlogie is now testing whether or not prolonged Revlimid maintenance could make a difference in outcome, so I am wondering what's our current thinking on the plateau? How long does one need to be in remission in order to feel secure that they are likely cured and what percent will reach this?

Dr. Frits van Rhee : I think the inflection points of the survival curve quite correctly pointed out _____ becomes progressively short in Total Therapy 1, 2, and 3 and it does appear to lie currently around seven or eight years on Total Therapy 3. In fact, the late relapses may still at times occur, can be expected even if patients are potentially cured. It is well expected the diseases like acute myeloid leukemia and Hodgkin's disease, etc., that late relapses occasionally do occur. So, we do sense that the data are holding up to manage cure date suggest that about, we suspect that the overall survival rate that's at 13 to 16 years will be in the order of 50%.

Nick van Dyk : And that's what _____ co-morbidity is from other ailments, right?

Dr. Frits van Rhee : Correct, yes.

Nick van Dyk : I don't want to cheat, but I have got one quick follow up that I would like to lob in, if you don't mind, Jack. I am going to charge in since Dr. van Rhee made quick business of the first one. So, I am four years in complete remission and UAMS has a highly sensitive test for minimal residual disease, which I am sure we will discuss, and I am negative for that, but I developed a monoclonal-like signature under



immunofixation about four months ago and Dr. Barlogie said he didn't know what this meant. I have subsequently looked into the Mayo research and they have looked at about 2,000 patients and have seen that about 35% to 40% of patients otherwise in remission do develop, what they call, a secondary MGUS and that this is actually associated with a much better overall survival because they postulated much like oligoclonal bands. This is an immune system rebuilding itself. I am curious as to whether or not you have seen that at UAMS. I would have expected that this would not have caught by surprise and I have encountered a number of other people with a similar situation, so it's not just my own biology I am asking about, but it does seem like this would be something you would be noticing there and I wonder if you thought you had any prognostic insight as to what it might mean.

Dr. Frits van Rhee : We have not yet done a systematic analysis of the oligoclonal bands. If you look at the Mayo paper in detail, it reveals that they have a mixture there of patients with oligoclonal bands and patients who have MGUS reestablishment after treatment for their myeloma. We have seen that here as well, we call it MGUS-like myeloma. In other words, patients who had a preceding MGUS were treated for their myeloma and MGUS remains. Then, there is the issue of oligoclonal bands. Oligoclonal bands usually means that there is immune reconstitution and you will see recovery also, uninvolved immunoglobulin, and that's generally considered to be a good feature and has a positive effect on outcome.

Nick van Dyk : So, in the MGUS, like the people that are treated and then develop MGUS, do they achieve complete remission and then lose it to this MGUS or does that MGUS eventually go away and is it the same M protein, I mean obviously that's the key question, can it be immuno panocytes against the original presenting protein? The patients that we call MGUS-like myeloma have the same original M protein?

Dr. Frits van Rhee : Yes.

Nick van Dyk : And usually the MGUS persists.

Dr. Frits van Rhee : Yes. In other words, it doesn't disappear. The oligoclonal bands obviously is a different situation. Usually in these long follow ups, the oligoclonal bands because there is immune _____ occurring, the oligoclonal bands eventually disappear.

Nick van Dyk : Got it.

Dr. Frits van Rhee : But the oligoclonal bands we see quite frequently here.

Nick van Dyk : Got it. Got it now. Okay. Thanks for indulging me.

Gary Petersen : Hey, Jack. It does seem like Dr. van Rhee is doing a really good job of not _____ questions, so why don't you ask both of your's?

Jack : Okay, I will. Dr. van Rhee, I had Total Therapy treatment in 1996 and there was no radiation involved and the only maintenance was interferon which was a blast for all, but my complete response only lasted for 18 months and yet I am still alive today because I ultimately had a full allo. So, my question in the stats that, for example, it was mentioned in the beginning about median survival of 15 years with Total Therapy. Would I be counted in that overall survival?

Dr. Frits van Rhee : Yes. Like in any study, overall survival includes salvage therapy. So, yes, you would be counted for overall survival. You would not be counted obviously if you have recurrence of disease and progression-free survival.

Jack : Right. Okay. That's what I thought and I just want to make sure that's how its done and then as I mentioned I got into a long-term remission from a full myeloablative allo in 1998, but its my understanding that Arkansas no longer does either full or mini allos. Is that true or do they do it just as salvage which was really salvage back then too?



Dr. Frits van Rhee : We currently don't do upfront allogeneic transplant. There was a time that we did a second transplant, the mini-allogeneic transplant for patients with high-risk disease and we did not see it improving in outcome and we did observe toxicities like chronic CHD. In multiple myeloma, the anti-myeloma effect on donor cells is more tightly linked to chronic graft-versus-host disease and its also not that potent. So, full myeloablative allografting _____ actually in abundance in myeloma _____ centers. A number of centers' studies have done an auto and a mini allograft. Some studies have shown slightly better survival for the allograft arm, others have not. I think that most centers do not perform an allograft upfront for multiple myeloma. One could make an argument that in very young patients with multiple myeloma, maybe in early thirds could set up for a graft_____. The way we define high-risk gene expression profiling that is a group of patients with usually highly proliferative aggressive disease and the _____ transplant is not potent enough to overcome that. So, apart from experimental studies which were tried on the anti-myeloma donor cells, in my view there is currently not a good role for allogeneic transplant upfront.

Jack : But you still do it in salvage therapy?

Dr. Frits van Rhee : We do not do it routinely in salvage therapies, in rare cases.

Jack : Thank you and Gary, I have another set of questions related to ASH, but I will wait until we go around again.

Gary Petersen : Okay. All right. Pat Killingsworth, your questions?

Pat Killingsworth : I am here and thank you for joining us, doctor. You have already answered a number of my questions. I was going to touch on the retrospective study that Mayo Clinic did on a large group of patients treated between 2002 and 2006 and it shows median overall survival of 10 years which is similar to TT results, I believe, but TT seems to be easing up on the throttle a little bit with the intensity of treating patients and I find it so fascinating now having been a patient almost seven years, watching the rest of the myeloma community move closer to what Total Therapy has been doing all along and they are starting to advocate getting myeloma harder upfront, so its interesting to see the two schools come together, but before I ask my question, do you have any thoughts on that? Did that sound correct?

Dr. Frits van Rhee : I think that's correct. I think people presently do embrace more and more the idea of some form of induction therapy _____ and one could argue about one or two transplants, some form of consolidation, and some form of maintenance, so lot of protocols and studies do have this sort of Total Therapy concept albeit perhaps _____ of treatment.

Pat Killingsworth : Sure, thank you. For disclosure purposes, I am a former Mayo Clinic patient and I understand that treatment decisions are very personal and I also understand why some experts and patients might feel that giving too much therapy might be just as bad as giving not enough; however, I am perplexed, I don't understand why your institution that's doing so much great work and has done so much great work has continued to come under fire. You have an opinion on some of your, if your studies are so closely monitored and audited and the results are the results, why do you think that a large part of the myeloma community continues to discount the work?

Dr. Frits van Rhee : I would say high trees catch a lot of wind. Isn't that? And we perhaps... (Laughter) And I think people also, in general terms, people don't appreciate how scrutinized these studies truly are. We really... No database is perfectly clean, but we really do make a major effort in collecting correct data, having it independently looked at. To the best of my knowledge, we are the only myeloma group who _____ an independent team of auditors to look at the data two or three times a year. So, the data are very well scrutinized and perhaps we haven't abdicated this very well or maybe this is insufficiently known.

Pat Killingsworth : How about the sharing of the data? Can that be part of it? Are you participating in the MMRF CoMMpass program or things like that? Is it that other institutions don't have access to the data?



Dr. Frits van Rhee : Obviously, the data gets published and all our gene expression profiling data is publicly available. We are not taking part in the CoMMpass project because our treatment approach is probably different, but we are always willing to share our results and I think we publish frequently and present frequently at national and international meetings.

Pat Killingsworth : Well, thank you very much for dedicating your life to help save our's and that words can't express how appreciative I am and I am sure our listeners are.

Gary Petersen : Thank you, Pat. Cynthia, Cyndi, are you online?

Cynthia : I am. Can you hear me?

Gary Petersen : Yes, I can. You got a couple questions for the good doctor?

Cynthia : I do. Thanks so much, doctor, _____ telling me so far. One of the questions I had just from listening to you is I am not quite clear exactly what gene expression profiling is and how that is different from other types of genetic testing? Can you explain the difference between gene expression profiling and maybe FISH testing and cytogenetics to make it more clear to maybe some of the patients on the line?

Dr. Frits van Rhee : Certainly. One is called metaphase cytogenetics, that means if you take a bone marrow sample, essentially grow it in the test tube and then you look at chromosomes under the microscope. The power of gene expression profiling is the chromosomes. The chromosomal material looks abnormal under the microscope, you can inspect old chromosomes. You can visually see all the genetic material. The disadvantage of metaphase cytogenetics is that at least in our hands its only informed in about 30% of patients. That means that the myeloma cells will grow in the test tube only in 30% of patients, that is because the remaining 70% of patients the myeloma cells need the bone marrow environment to grow. So, in those patients the metaphase cytogenetics are normal and non-informative. Only in patients with more aggressive disease, the myeloma cells can survive and grow in the test tube. The other test is called FISH or fluorescence in situ hybridization. Essentially what FISH does is take a specific probe or a number of specific probes and try to identify specific abnormalities. The advantage of doing FISH is that its informative in all patients. The disadvantage is that you can only look at a limited number of specific abnormalities. In other words, you can look for a missing part of chromosome 13 or 17 or an additional part of chromosome 1, but again its limited to what you look for, limited to the probes that you use. Gene expression profile looks at purified myeloma cells. Its informative in a majority of patients and you look at the expression of all genes in the purified myeloma cells and you can look at expression model and see whether they are over expressed or under expressed. Then, you can do the molecular picture of the myeloma. So, it is much more sophisticated in looking at the expression abnormalities of genes than the cytogenetic or FISH studies.

Cynthia : Yeah. Is the gene expression profiling done at the beginning of diagnosis or is it done periodically like a bone marrow biopsy or a blood test or...

Dr. Frits van Rhee : Its collected from the bone marrow, we do it at diagnosis and we certainly also do it at relapse to see whether the profile has changed. We also do gene expression profiling on whole biopsies, that is the whole actual piece of bone which is being taken out, not just to purify plasma cells and that is presently ongoing research.

Cynthia : Okay. Thank you. I think I have a better understanding of that now. Another question I have is I am always concerned with aggressive high-dose chemotherapy protocols, including the tandem stem cell transplant because of the risk of secondary cancers like the MDS or the AML and also maybe sometimes they drill into bone marrow so that you couldn't get other types of treatment and I heard you say you have a lot of long-term _____ on your Total Therapy patients, I was wondering if you continue to monitor them for MDS or AML or leukemia-like diseases and if you have seen an increase in number of patients?

Dr. Frits van Rhee : Yes. I think that's an excellent question. Both in our center and in other studies, we



think introduction of immunomodulatory agents, we have observed an increase in both what we call cytogenetic MDS, in other words only the chromosomes look abnormal _____MDS which occasionally transforms into myeloid leukemia. That incidence is low but has increased with introduction of immunomodulatory agents such as thalidomide and Revlimid. Patients are being monitored for this long term and at the moment in most studies, the benefits of using maintenance with immunomodulatory agent outweigh risks, but it does raise the question how long the maintenance therapy should be and I predict that in the future we will see shorter duration of use of immunomodulatory drugs.

Cynthia : We are thinking that the increased incidences due to the maintenance with the IMiD, not the high-dose chemotherapies that are used in the stem cell transplantation and induction that you are using.

Dr. Frits van Rhee : No. It may be that some patients already have in their normal bone marrow, not in their myeloma cells, but their normal cells already have some abnormalities which occur in MDS and post transplant, the bone marrow functions on a reduced number of stem cells and there is a greater chance that an abnormal MDS clone may emerge and that may be facilitated by the use of immunomodulatory drugs. So, that's our current thinking. We find that the infusion of more stem cells seem to be protective against developing MDS post transplant.

Cynthia : Okay. Thank you for that. And one other question I have is, is there Total Therapy _____ for maybe patients who are transplant eligible but the body might not be able to take the full blunt of the Total Therapy program and if there is, what kind of supplementation would that be?

Dr. Frits van Rhee : I think that's an excellent question. Obviously, not everybody is suitable for a Total Therapy approach. In those patients, we actually try to personalize treatment more. We may reduce doses of chemotherapy. We may reduce the dose used at the time of transplant. We may only do one transplant. Sometimes in those patients who are frailer, we would skip consolidation and give less intensive maintenance therapy. So, we do, in frailer patients, try to tailor the treatment to the comorbidities that the patient has and obviously not every patient is a transplant candidate and sometimes even younger patients, there's a lot of other medical problems who really should be managed with an approach to control the disease rather than a more intensive approach.

Cynthia : Okay. Thank you so much for answering our questions.

Gary Petersen : Yeah, as a followup to that question and in Total Therapy, what percentage of your patients are on a protocol like that versus you know the total patient population? So, for Total Therapy 1, 2, 3, you know its about a 1,000 patients, I guess, or so, right? So, is your total patient population a couple thousand, 3,000, so are 30% of the people on Total Therapy protocol?

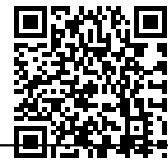
Dr. Frits van Rhee : Yeah. We enroll in the order of 30% of our referrals on a protocol and obviously our referrals are a mixture of newly diagnosed and previously treated patients. So...

Gary Petersen : They can't be on protocol, right? They can't be on a TT program, at least off protocol again because...

Dr. Frits van Rhee : We do have a Total Therapy program for previously treated patients, we call it Total Therapy 6. They get the same treatment as Total Therapy 5. Rationale for doctors is that patients who have been previously treated_____ for patients with high-risk disease. The _____ for Total Therapy 6 stipulates the patient must have had more than one month of prior treatment, that they should not have had a stem cell transplant.

Dr. Frits van Rhee : Okay. Nick, you said you had another followup?

Nick Van Dyk : I actually wedged that one in earlier, so I appreciate the opportunity but I have used my time up. Okay. I have another question, if that's okay.



Dr. Frits van Rhee : Sure.

Nick Van Dyk : So, if I am understanding correctly, since I am not a newly diagnosed patient and I have already had a stem cell transplant, will I be able to be treated at all at Arkansas or are my treatment options from Arkansas out?

Dr. Frits van Rhee : Obviously, we treat a lot of patients like much yourself, who have had a transplant elsewhere, relapse, and then come to Arkansas for treatment. So, we don't confine ourselves to treating patients who have never had a transplant. A lot of our referrals are patients with relapse disease after transplant elsewhere.

Nick Van Dyk : _____ Total Therapy program _____ salvage.

Dr. Frits van Rhee : It depends how long you relapsed after transplant. If you had your transplant 10 years ago and you have had a remission of 10 years, you could sort of start over again and give them more extensive type program in the younger patients. Obviously if you have relapsed relatively shortly after a transplant, we are looking more towards doing salvage therapies. In some patients, we do a further transplant, particularly patients who are longer than three years out after their last transplant.

Nick Van Dyk : Okay. Thanks so much.

Gary Petersen : Priya, do you have any questions?

Priya Menon : Yes. So, audience, if you have questions for Dr. van Rhee, please press 1 on your keypad and we can bring you live on air to ask your question. I have with me some of them, I'll ask them. Doctor, one of our participants has written in asking after fracturing my femur in June, I was diagnosed with myeloma. Since then, I have not had crab but after radiation on the femur, my kappa light chain has shot through the roof and then _____ was detected. Now, I am not sure of the next step. Stem cell transplant, chemo, and if so what kind?

Dr. Frits van Rhee : So, as I understand, we are dealing with a patient who has fractured the femur, that has been repaired and only has had radiation therapy. Correct?

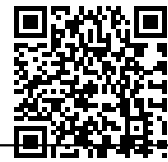
Priya Menon : Yeah. Sounds like it, yes.

Dr. Frits van Rhee : Yeah. First of all, it needs to be established that the patient has an isolated plasmacytoma, that is only plasma cells growing in one area in the femur. In that case, you would not need any further treatments _____ the patient who is fit and younger _____ patient, we would consider for Total Therapy-type approach.

Priya Menon : Thank you. We have another question. This person wants to know more about kappa and light chain numbers and what they mean.

Dr. Frits van Rhee : Okay. There are two ways of monitoring myeloma in the blood. Myeloma cells are plasma cells and the job of normal plasma cells is to make antibodies. An antibody comprises of two heavy chains and two light chains bound together and that is the whole myeloma protein which you measure in the blood. Its referred to as the M protein or the M spike or the myeloma protein. Some patients have myeloma cells which only make light chains and these cells have lost the ability to either make the heavy chain and put the four chains together and in those patients you can monitor disease with the light chains. Quite often, you will find the patients have myeloma cells which make light chains and other myeloma cells which may make the whole M protein, so in fact you have two tumor markers that you can measure – the whole M protein and the light chains only.

Priya Menon : Thank you, doctor. This third question asks, did the ASH meeting last week give you any



hope for a cure in the near future?

Dr. Frits van Rhee : First of all, I think that we currently already have the available drugs to cure at least some patients, which is really good news for the myeloma community. What I find one of the exciting things happening in the cancer field is the ability to manipulate the immune system. Their antibodies _____ tumors which take the break of the immune system and accelerate immune cells against cancer. This is something which is also now being introduced into the blood cancer field. These antibodies could potentially be combined with vaccines or they could be combined with immunomodulatory drugs, but I think that's an exciting development. The other new development which is earlier on in its clinical application is the development of immune cells which are specifically targeted through cancer cells and are highly activated and particularly in pediatric acute leukemia with some very exciting studies conducted. So, I think there will be increasing ability to manipulate the immune system in a way that is therapeutically very powerful. Then, the other, I think, interesting observation is that we are better at predicting nowadays with which patients with very early myeloma, what we call smoldering disease, are likely to progress to really myeloma and you can pick out these patients at high risk of progression and they seem to benefit from early treatment. So, there will be increased interest in the coming years of treating patients with what is called smoldering disease at an earlier stage.

Priya Menon : Thank you very much, doctor. Gary, I think we have time for a quick last round if any of the panelists have questions for Dr. van Rhee.

Gary Petersen : Yeah. I know Jack had another question that he wanted to ask about ASH.

Jack : Actually, Gary, mine was answered, but thanks.

Cynthia : Gary, I have a question.

[00:56:33] Okay.

Cynthia : _____ few of my friends have been diagnosed with, I guess, a very serious type of myeloma, the leptomeningeal myeloma, when the myeloma crosses the blood-brain barrier I understand and I understand there is not many treatments that will help with that. What would someone in Arkansas do with a patient that has leptomeningeal myeloma?

Dr. Frits van Rhee : We would give them chemotherapy and inject chemotherapy well into central nervous system, in the spinal fluid. Usually we use a combination of three drugs and a series of treatments. When patients have leptomeningeal myeloma disease in the central nervous system, sometimes what's called the blood-brain barrier is broken and some of the chemotherapy which is given systemically can penetrate there. It has to be said that myeloma in the central nervous system is a very serious situation and usually seen in the end stages of the disease and its very difficult to treat.

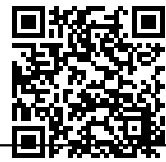
Cynthia : Okay, so there are _____ chemotherapy that can be directly injected into the central nervous system. Is that what you said?

Dr. Frits van Rhee : Yeah. Into the spinal fluids, yes.

Cynthia : Into the spinal fluid. Is that part of the nervous system? I am not _____ biology.

Dr. Frits van Rhee : The spinal cord lies in a sac and the sac contains fluids. We can access this sac by going between vertebrae and injecting chemotherapy into the spinal fluids. The spinal fluid surrounds the spinal cord and can treat the disease.

Cynthia : And would it be the same types of chemotherapy that are normally used to treat myeloma or all different type of chemotherapy?



Dr. Frits van Rhee : Typically what we use are drugs which are used in, one drug which is used in leukemia, methotrexate. We do give steroids which is given in myeloma. Then, we use a drug called _____ sometimes and sometimes a drug called _____. Both drugs are not typically used upfront in myeloma therapy.

Cynthia : Thank you so much.

Dr. Frits van Rhee : They are drugs more used for aggressive leukemia and usually patients with myeloma in the spinal system have very aggressive disease.

Cynthia : Yeah. Thank you so much.

Gary Petersen : Doctor, thank you so much. It looks like we are coming to the very end of this and my thought coming into this is that you are going to be exceptional and you were exceptional. You did a great job. You went through all of our questions. I don't think that's happened ever since we have done this and you were succinct, very to the point, and did a very great job of simplifying the TT program or Total Therapy program at Arkansas and also answered a lot of the questions about, you know, why that tree is getting all the wind.

Dr. Frits van Rhee : Thank you for having me on the program and its a pleasure to speak to you now and I hope that benefitted the listeners.

Priya Menon : Thank you, Dr. van Rhee, for joining us today. It was a pleasure to have you here. Gary, Pat, Jack, Nick, and Cyndi, it was a great discussion and thank you so much for making this such an informative forum. Dear audience: Thank you for your support and we look forward to having all of you join us in the new year 2014. We have lined up interesting shows for you. Myeloma panel will feature MMRF on 28th of Jan and our cancer and nutrition series, we have our panel with Dr. Donald Abrams of UCSF and is co-hosted by Pat Killingsworth, its being scheduled for 17th Jan. Please visit curepanel.carefeed.nic for more information on our upcoming shows in the new year. To search for myeloma trials, please use MMRF trial search tool at myeloma.trialx.com/ _____. The link for today's show will be sent via email to all participants. Thank you. Happy holidays and meet you all in the new year. Thank you.

Gary Petersen : Happy holidays. Merry Christmas. Happy Hanukkah. Happy new year.

Dr. Frits van Rhee : Good health to everyone. Bye, bye.

Thanks. Bye, bye.