Myeloma with MD Anderson's Dr. Orlowski

Shoot for a 100% complete response is what doctors are aiming for and this may soon become a reality with new drug combinations which are showing a lot of promise, informs Dr. Orlowksi. Newly diagnosed patients to high-risk patients, Dr.

Orwloski and the panel cover all new drugs as well as drug combos which are in various stages of clinical trials. A compelling hour of a whole lot of useful information and Dr.

Orlowski even announces his email on-air!

Full Transcript: Priya : Good evening, everyone, and welcome to the Cure Panel Talk Show on multiple myeloma. I am Priya Menon, Scientific Media Editor at Cure Talk, and along with the Cure Talk team of Sharib Khan and Chintan Patel, I welcome all of you this evening to a discussion on multiple myeloma. As always, we will be moderating the call and bringing people live on the show. As most people here know, Cure Panel Talk Show is organized by Cure Talk, the blog of trialx.com, an online platform to connect patients to clinical trials of new treatments. For information on clinical trials for all conditions, please visit trialx.com/ask. For information on myeloma clinical trials, please visit the MMRF trial site, myelomatrials.org or myeloma.trialx.com/ask.Cure Panel Talk Show started its journey with discussions on multiple myeloma and we are happy to say that we have grown with you and are now conducting panel discussions on prostate cancer, yoga, and mental health too, which will debut in May. Our broadcasts have been replayed over 38,000 times. I would like to take this opportunity to announce Cure Panel's first live on-air myeloma support group meeting scheduled for May 15th, 6 p.m. EST. Pat Killingsworth is part of the new initiative and will be co-hosting the meetings with us. Myeloma patients, caregivers, and family members can register and dial in to share their stories and seek support from experienced myeloma support group leaders. For more information, please visit Cure Talk website.

This is the 10th episode of Cure Panel Talk Show and the 8th time we are discussing multiple myeloma on this platform. We are honored to welcome renowned myeloma specialist, Dr. Robert Orlowski from MD Anderson as the expert speaker on today's Cure Panel Talk Show. Welcome to the show, Dr. Orlowski. Gary Petersen, editor, myelomasurvival.com will be co-hosting the show with me today. Welcome, Gary! On the panel, we have noted myeloma blogger, author, Pat Killingsworth; myeloma survivor, activist, Jack Aiello; and myeloma survivor, musician, blogger, Nick Van Dyk. Welcome to the show, gentlemen! Registered participants, please take note, we have received many questions for this panel and for making optimum use

of Dr. Orlowski's time and providing answers to most of them, we have consolidated the questions and re-phrased them. Our paid panelists will be discussing these questions with Dr. Orlowski in addition to their own. Before we begin, I would also like to read out a couple of rules. If you are listening in to the panel through your phone as well as computer, please mute or stop the online broadcast on your computer for better audio quality. Callers will be invited to ask questions at the end of the discussion. They can let us know by pressing 1 on their keypads and we will bring them online live. Gary Petersen will now introduce us to the expert and panelists and begin the discussion. Gary, you are on air.

Gary Petersen : Okay. Well, thank you so much, Priya, and first and foremost, we would like to thank you and everybody at Cure Talk for bringing this forum to us and also I would like to acknowledge all the myeloma patients, caregivers, and certainly the panel members. The panel consists of Pat Killingsworth and Jack Aiello and Nick Van Dyk. We are all myeloma survivors, Jack little bit more than most. Pat 5, Jack 17 years, and Nick 5 years. Pat also has a blog by the name of www.multiplemyelomablog.com and I think its one of the best. Also, Nick has one of the very best as well. Its an informative blog that details his myeloma journey. His blog is www.nvdmyeloma.blogspot.com and in his spare time he runs a rock band and holds an executive position at a major corporation. Jack is also very much an activist for multiple myeloma and so I thank all of you for being part of this and being part of this for so long. I think all of our panelists have one thing in common and that is that we all have been treated by some of the very best multiple myeloma specialists in the world and one of those very skilled myeloma professionals happens to be with us today for this, you know, for this presentation and I welcome Dr. Robert Z. Orlowski and what I would like to do now is introduce him and just say a little bit about his bio and I have to give you the clip notes version of his bio because he does have quite a list here and I just wondered to myself how large his business card must be, must be 8.5 x 10, glossy.

Dr. Orlowski is the Director of Myeloma and the Professor of Medicine in the Department of Lymphoma/Myeloma and Experimental Therapies, Division of Cancer Medicine at the University of Texas MD Anderson Cancer Center in Houston, Texas. He is board-certified in internal medicine and medical oncology. Dr. Orlowski earned his degree in molecular biophysics and biochemistry from Yale and his medical degree from Yale University School of Medicine, but he completed his internship at another superior institution, Barnes Hospital at Washington University, one of the top 10 cancer centers in the world. If you look at US news and world reports, they will say that the number one cancer center in the world is MD Anderson and we are just so blessed to have Dr. Orlowski with us today. He also has an excellent twitter paper called Multiple Myeloma Daily and it is published on his twitter feed, Robert Z Orlowski @ Myeloma_Doc or you can just, you know, in the twitter search, hit Robert Z. Orlowski and you'll find it. Also includes onus is his title in the twitter account says he is a translational researcher who hates myeloma, so nothing better than a doctor who is putting up the good fight. So, doctor, with that introduction, please feel free to talk about new therapies and new combinations. (Pause) Doctor, you are on.

Dr. Orlowski : Ah, Gary, there you are! Thank you very much for the kind introduction and thanks also to Priya and Pat and Jack and Nick for putting all of this together. I think this is going to be hopefully an exciting program for patients. Its a great opportunity for me also to give you some updates because many of you may know that earlier this month in April, there was the most recent meeting of the International Myeloma Workshop which happens every two years and allows those of us in myeloma to update each other on some of the exciting developments and I wanted in particular to focus on combination regimen because I think there is increasing data and an increasing feeling in the field that combination regimens are going to be the best way to get us closer to a cure for myeloma. For people with newly diagnosed disease, some of the current standards of care are two and three-drug combinations and examples include bortezomib and dexamethasone or lenalidomide and dexamethasone as two-drug combos while commonly used three-drug combos are bortezomib with lenalidomide and dexamethasone and also bortezomib with cyclophosphamide and dexamethasone. These all work very well, but none of them yet achieve a 100% complete response rate, which is, of course, what we would like to shoot for and there are some exciting new combinations that some people may be aware of and others that are coming that I thought I would briefly mention. For newly diagnosed patients, one of the exciting combinations is lenalidomide and dexamethasone with carfilzomib and, as you know, carfilzomib, like bortezomib, is a proteasome inhibitor and there is one early phase I and II

study that's been published, that shows that the three-drug combination with carfilzomib has almost a 100% response rate and it looks like maybe there will be better quality responses, meaning more patients in a complete remission, but right now the US Cooperative Group Network which includes the Southwest Oncology Group, the Eastern Cooperative Oncology Group, and also the Alliance are doing a study which is comparing lenalidomide and dex with bortezomib to lenalidomide and dex with carfilzomib as an initial therapy and for those of you who may be recently diagnosed, this may be a trial that you would want to participate in because hopefully we will be able to advance the field with it.

The other area in the upfront setting where we still need a lot of improvement is for patients with high-risk disease and these are people in particular who have high-risk features, including some chromosome abnormalities. One example is deletion 17p by FISH or fluorescence in situ hybridization and also a high-risk signature on the 7D gene panel which was developed by the folks at Arkansas, which is now available as a test that you could get right now. These people still, despite our best therapies, have only about a three-year average survival. Fortunately, only about 15% to 20% of patients with myeloma are high risk and the rest of folks are standard risk and do much better, but we still need to improve things for those high-risk people and the current trial which the Southwest Oncology Group is leading is comparing what we think is our current best treatment, i.e., bortezomib with lenalidomide and dexamethasone followed by maintenance with all of those three drugs as well and that's the control arm or standard, if you will, and the experimental arm is adding a drug called elotuzumab to bortezomib, lenalidomide, and dexamethasone. Elotuzumab is another really exciting drug, I am sure you have probably heard about it. Its an antibody which attaches to the surface of myeloma cells and acts as the flag, if you will, to signal to your immune system to say, here's the fellow that you need to come and destroy. So, the benefit of this is that because these antibodies really help to stimulate your immune system, its a much more targeted therapy and generally have fewer side effects than would be the case with a small molecule and we're really looking to see if in these high-risk patients, the four-drug combination is better than the three-drug combination. Also in the newly diagnosed setting, there are some exciting studies looking at oral proteasome inhibitors and there is a drug called ixazomib which is not so easy to say but easy to take because its an oral version of a proteasome inhibitor and there is a study ongoing looking at that drug with lenalidomide and dexamethasone as an initial therapy and the early reports of that study have been quite positive at the workshop and the benefit of this, of course, is that its an all oral combination for initial myeloma therapy which would be really exciting because the quality of life for patients will always be better if they can stay at home and get therapy there as opposed to having to slip in to the clinic or the doctor's office to get injections.

Couple things I thought I would say also about what can be done in the relapsed and also possibly refractory setting. I am sure all of you know about the recent approvals of carfilzomib for relapsed and refractory myeloma in July of last year and then in February of this year, pomalidomide was approved and any time we get new drugs available, that's going to be a huge benefit for patients, but one of the things we always like to do is to combine drugs together that make great sense and so at MD Anderson here we have led a study through the Academic Myeloma Consortium, which for patients with relapsed or refractory myeloma combine carfilzomib and pomalidomide together and the updated data which were presented at the myeloma workshop showed that this combination had a 77% response rate in relapsed or refractory myeloma and this could be given with the standard doses that have already been approved, including 4 mg for pomalidomide and the carfilzomib at 20 and then 27 mg/m sq. So, this study is continuing to make sure that we, as well as possible, understand the safety as well as the efficacy, but one of the pluses of this approach is that you can actually use this combination off of a trial because both of the drugs are already FDA approved. So, for those of you that are in the relapsed setting or refractory setting your doctor could have the option to do this even if you can't come to one of the centers that is involved in the trial.

One other combination that we have tested at MD Anderson, that you can also get without a trial, is the combination of lenalidomide with thalidomide and dexamethasone and we actually put those together based on laboratory studies we did that showed that one of the mechanisms by which myeloma cells become resistant to lenalidomide can actually be overcome by adding thalidomide. So, we put the three drugs together, again in some all-oral combination, and what we found is that even in patients whose disease had previously progressed on lenalidomide 50% to 60% could respond to the three-drug combination of

lenalidomide with thalidomide and dexamethasone and so that again gives you another option.

And then, finally two other drugs that I think are very worth mentioning for people in this setting to look for – one is the drug called daratumumab. It sort of sounds like elotuzumab because it also is an antibody, but it binds to a different protein on the surface of myeloma cells than does elotuzumab and like elotuzumab, what daratumumab does is it helps your immune system find a good target which in this case is myeloma and that's shown a very nice response rate even in patients with very advanced myeloma and there is going to be a large study of this drug, which if it were positive could lead to its approval, which would hopefully be our second antibody for myeloma because probably elotuzumab will be approved before that and then finally one other drug to mention is a drug called don't-yet-have-a-name, but its called ARRY-520. This is a drug that targets a protein known as kinesin spindle protein, which is important in division of myeloma cells. If you inhibit that protein, the myeloma cells can't divide and that results in their death. One of the advantages of the drug is that there's absolutely no neuropathy with it because the target protein is not expressed in nerve tissue and there are very nice data showing that this drug either alone or with dexamethasone or with carfilzomib shows very good activity even in patients who previously have had and their disease has grown through drugs like lenalidomide and bortezomib and dexamethasone and there will be larger studies of this drug coming, which will be performed across the country and so hopefully those of you who need new therapies can look for those and hopefully they will be open at a center near you.

So, just to sum up, I think that in the past there's been a discussion in the myeloma field about whether its better to use one or two drugs and save others for later in the disease course or whether its better to use combinations as early as possible and this applies both to newly diagnosed patients as well as people whose myeloma has relapsed and I think the debate is still ongoing because we don't fully know the answer, but my feeling and probably the feeling of many people in the field now is that it is better to move forward with combinations because combinations work better than either one drug by itself or two drugs by itself if you are using a three-drug combination as the comparator. Of course, these are not for everyone because unfortunately some folk because of complications of their disease or other medical problems may not be able to do well with three or four-drug combos, but for those who can those are probably the best ways to go and that will be my summary and I will turn it over back to Gary and to Priya.

Gary Petersen : Well, thank you so much, Dr. Orlowski. I imagine you enjoyed the blossoms in Kyoto, Japan.

Dr. Orlowski : But definitely, oh, and by the way, my business card is regular size, not 8.5 or 11. (Laughter)

Gary Petersen : Okay. Umm… What we did is we had a number… Actually, we have got a full house today with all of the spots that were available taken and we had so many questions and a lot of them overlapped and both Jack and Nick were kind enough to go through and turn 22 questions into 11 questions. Nick did little Disney magic on it and the only thing is I think the word count went up, but the number of questions went down, but we will go through those right now. I will start out with question no. 1 and then we will go on from there.

So, the very first question that we will be discussing today is kind of a verbose one, but its also q very, very important one and it is that there are numerous schools of thought about if and when to do transplants and you didn't mention transplants at all during this discussion, so I would be interested in finding out your thoughts on that and whether to do one transplant or two and whether or not to have expensive maintenance therapy afterwards, saying that all schools of thoughts begin with one or more of the so called novel agents, Velcade, Revlimid, thalidomide in conjunction with a steroid. One school of thought then seems to keep on these and other novel agents alone and forego a transplant, rather a Berenson approach until these agents fail. Another approach is called the middle ground approach, seems to be used as protocol until the disease has been suppressed as much as possible, ideally to remission and then transplant at the time and potentially follow it up with maintenance therapy and I guess that would be kind of Mayo approach, while the third school of thought is used in only one or two cycles of induction, including old-line chemotherapy drugs like Cytoxan in addition to novel agents and then doing two transplants back to back and following up with

extensive maintenance. This would be kind of the UAMS or Little Rock approach. What in your mind are some of the most pervasive arguments for or against novel agents without transplant, single transplant with or without maintenance, and 3, tandem transplant with extensive maintenance? Which of these protocols is the best first-line approach to a newly diagnosed patient and does age or risk factors influence this in your mind? I know that's a lot to say and hopefully you can kind of slice and dice through that.

Dr. Orlowski : (Laughter) Well, thanks very much, Gary. I should say these questions are all outstanding and just quickly because we probably won't be able to get to all of them because I usually am verbose in my answers. I thought I would let your listeners know. You have already mentioned my twitter page and also they would be more than welcome to email me directly with any questions and I promise to try to get back with them in a day or two and my email address is rorlowsk@mdanderson.org. So, let's get to the questions. There's a couple sections in here. Let me try to tackle them in pieces.

One question is about tandem transplant versus other approaches and certainly tandem transplant as pioneered by the French and also by Dr. Barlogie at Arkansas was an outstanding approach in a time when we had less effective chemotherapy drugs that were unlikely to induce a complete remission by themselves as part of induction. When you look at some of the studies that compare one versus two transplants though, several of them suggest that the people who benefit from a second transplant are the ones who are not in a complete remission after the first one and because our induction or upfront therapies are now so much better, that suggests the possibility that if you are in a complete remission or very close to a complete remission after the first transplant, that the second one may not really be of huge benefit and I think that that probably would be my answer to whether old-line chemotherapy plus the tandem transplant is better, but frankly we don't know the answer to some of these questions and there is one large trial that's currently ongoing in the US which is comparing bortezomib, lenalidomide, and dexamethasone induction for everybody and half of the patients get stem cells collected and then early transplant while the other half gets stem cells collected but have transplant only at the time that their myeloma relapses after their front line therapy and that may help to explain which of the approaches is better, i.e., what you dubbed the Jim Berenson approach, meaning to give a few drugs that are novel and do induction but save transplant until later versus the so called Mayo approach, as you dubbed it, of using induction and then transplant. For me, if patients have an option, I tend to feel that myeloma cells are most sensitive to chemotherapies at the time that patients are first diagnosed and therefore it makes some sense to use induction chemotherapy and then follow it with a stem cell transplant and maintenance as part of a package. Up to now, there are no randomized studies that show that a chemotherapy-only approach as part of front line without transplant gives you the same or better outcomes as you get with a transplant. So, I would probably still be in the group that would recommend induction chemo, transplant, and then maintenance, but of course, this has to be individualized, then it depends on what each patient's risk is, as you pointed out, and also on what each patient's individual wishes are. So, I always have a long discussion with patients and we often then come up with different recommendations based on that discussion.

Gary Petersen : Well, that… Thank you very much for that question and also I wanted to thank you so much for providing your email address to all of our listeners. That is… That is fantastic! I didn't expect that. I don't think that your patients expected that and that was… That's remarkable on your part and I thank you so much for that. Pat, its your question. (Pause) Pat Killingsworth, are you…

Pat Killingsworth : Yes. Can you hear me, Gary?

Gary Petersen : Yeah, I can.

Pat Killingsworth : Great. Great. My (unclear audio) isn't that the way it goes? Hello, doctor! Has anyone worked on combining the two immunotherapy drugs?

Dr. Orlowski : You mean for example, lenalidomide and pomalidomide?

Pat Killingsworth : No, no. Elotuzumab and the "d" drug? (Laughter)

Dr. Orlowski : Well, elotuzumab right now is being studied both in combination with lenalidomide which looks like a very active combination and in combination with bortezomib, which looks exciting as well. So, I think that elotuzumab in general looks like a very active drug and any of those combinations will probably result in excellent benefits. Also…

Pat Killingsworth : Sure. I just wanted to… If anyone has had combined the two immunotherapy?

Dr. Orlowski : Oh, now I understand your question. So, you know, that's a great question. Would it be nice to combine elotuzumab and daratumumab and look at maybe adding lenalidomide as well because lenalidomide adds to the efficacy of these antibodies and right now nobody is doing that yet because neither of the drugs are FDA approved. I think that would be very exciting and one would hope that by targeting the myeloma cells even better with two different antibodies that the outcomes would be improved and maybe that's one way we could get away in the future from some of the cytotoxic chemotherapy drugs.

Pat Killingsworth : Sure. Well, that's exciting and hopeful. Thank you. I had a question here from one of my readers when they heard that you were going to be featured on the show and you had written something about advanced treatment options. Apparently, I am not sure where this was referenced, but it says for years the standard approach to multiple myeloma has been high-dose chemotherapy to wipe out the bone marrow of the cancer cells, followed by a stem cell transplant, but MD Anderson is among the select few centers that are pioneering your options that have less impact on your body. Many patients are having remarkable success and of course these options include immunotherapy, a new message for stem cell transplant patients. So, I think his question was, he said I was intrigued by the suggestion that Anderson was moving away from transplant as primary treatment and also by the mention of newer methods of transplantation. Could you comment on that briefly?

Dr. Orlowski : Sure, be happy to. Well, one of the things that we are doing in the immunotherapy category which right now is being added on to transplant is a study which is part of our spore in multiple myeloma, which is a brand funded by the National Cancer Institute and what this trial is doing is we take patients and actually isolate their M protein or monoclonal protein from the blood before they go to transplant and we use that protein as a vaccine which also includes treatment after transplant and the idea is to try to train their immune system to destroy the cells that are making this M protein, which of course are only the myeloma cells and so that's, I think, a very exciting approach because the immune system is something we haven't really used as much as we should against myeloma. We still, as of course I mentioned, do this in the context of transplant and at least for right now, we are not moving away from a transplant approach, but I do think that some of these immunotherapy approaches, if they were to work in patients after transplant, could also be employed for patients before transplant to see if perhaps we could at least in some patients, avoid the need for a transplant.

The other study that we are going to be doing has to do with the so-called chimeric antigen receptor T cells and that's another way of retraining a patient's T cells, which is part of their lymphocyte fraction in the blood to attack myeloma cells. So, those are two things that we are doing that hopefully will improve upon what we are able to do now with just drug therapy.

Pat Killingsworth : Well, thank you, doctor. That's great! I will turn the ball over, I believe, to Nick or to Jack. Hi, Jack!

Jack Aiello : I am here. So, I have a question related to clinical trials. Having been diagnosed 18 years ago, I have participated in a couple of them and always encourage patients who talk to me to at least consider them, but they are asking the questions usually about how extensive placebos or control arms are used in myeloma studies and clinical trials and, doctor, what would you say to encourage patients to participate in clinical trials but they are worried about receiving placebos?

Dr. Orlowski : Yeah. Well, you are making a great point about placebos and patients do always worry about whether they will be on a placebo or not. In the vast majority of phase 1 and phase 2 trials, placebos are not

employed and if they are, the patients by law have to be informed by the physician and the research nurse of that and the consent form, although I know that often they are quite long and not always written in as simple a language as they should be, the consent form has to mention the possibility of a placebo. Where occasionally placebos are used are in the context of phase 3 trials. These are studies where a standard regimen is being compared to the standard regimen plus a new drug and sometimes the control arm which is getting just the standard also has a placebo added to it, the thought being that the doctors who are treating patients will therefore not know whether patients are on the standard arm or on the placebo arm, but even the placebo arm usually is not placebo alone but a combination of the standard of care. For example, I mentioned one of the studies earlier of ixazomib plus lenalidomide and dexamethasone as an upfront treatment for myeloma. In that phase 3 study, the standard or control is the lenalidomide and dexamethasone plus a placebo, while the experimental arm is lenalidomide and dex plus ixazomib. What that means is that even if you are randomized to the standard arm, which does have one of the three drugs as a placebo, you are still getting the standard of care. So, you never would have placebo alone in these studies. You are always going to have a standard plus a placebo or a standard plus the new drug and so hopefully that will reassure patients. The other thing, of course, is that many of the most exciting drugs right now, which are not yet FDA approved are only available on clinical trials and the models that we have in the laboratory now for testing drugs are much better than they used to be, which means that by the time a drug comes to a clinical trial, its usually been shown to have very good activity against a number of myeloma models and although that doesn't guarantee that the drug will work in an individual patient, it at least increases the chances. So, I think that participating in trials is an important part of myeloma therapy and I agree with you, patients should always at least ask about what their trial options are.

Jack Aiello : Thanks very much. I definitely agree with your comments there and I will turn it over to Nick.

Nick Van Dyk : Hello, can you hear me? Excellent! Thanks, doctor, for joining us. This is another of the multi-part questions, I am afraid. I am sure many on this call noticed the IMF's press release about its Black Swan initiative, the goal of which is to design a test that will determine the presence of any post therapy residual disease. So, my question here is, is the announcement of this initiative effectively a recognition that some patients might be being cured through current protocols and how sensitive must this test for minimal residual disease be to provide confidence and with accuracy and then lastly, Arkansas has implemented a multi-flow psychometry test for minimal residual disease that was developed in conjunction with researchers in Salamanca because this test intersects with any test that might be employed by the IMF.

Dr. Orlowski : Well, minimal residual disease is certainly a hot topic in myeloma, as you have pointed out, and really its a recognition that the old ways of measuring response, for example, we used to measure complete remission by just a 75% reduction in the M protein or monoclonal protein. Then, when our drug got better, we made complete remission 100% reduction in the monoclonal protein, which certainly felt more logical, but we still know that people in a complete remission have evidence of myeloma which is below the level of detection of the protein electrophoresis and immunofixation, which has been the standard test. So, there are a number of approaches which are more sensitive to detect what's called the MRD or minimal residual disease. These can be flow cytometry, as you mentioned, which is basically a way to fingerprint cells from the bone marrow or blood and try to identify whether plasma cells are normal or whether they are abnormal myeloma cells. Another assay that is commonly used for research purposes is polymerase chain reaction or PCR, which looks for changes in the chromosomes that are typical for myeloma and the other test which is still getting started but looks also interesting is what's called whole genome sequencing where you can actually either from the blood or from the marrow collect cells and do sequencing of the entire series of chromosomes and identify which cells are normal and abnormal and how many of those there are. So, all of these are ways to try to detect whether a patient who is in complete remission by the old blood and urine criteria may actually be at a point where they are cured because we do know that up to 10% to 20% of people stay in complete remission after transplant even up to 10 years out and they may be cured. So, the question really is whether we can use these techniques to identify lower amounts of myeloma or are some of those people cured and if we detect lower amounts of myeloma, the next question is can we show that additional treatment of the people who have those low levels will be of benefit or maybe those are people who we could leave alone and their myeloma will slowly decrease over time, possibly with immune-mediated

therapies.

Nick Van Dyk : That's an excellent comprehensive answer. Thank you.

Gary Petersen : My next question is when testing or a degree of risk in myeloma, there are numerous methods ranging from FISH to the 70 gene array and now minimum residual disease. There are also general assessments of risk based on less precise measures, for example, IgD versus IgM or light chain disease versus other types. You have already mentioned some of this. Which type of assessments do you find pervasive and why and how does risk determine which protocol you would likely follow given the three approaches outlined in the previous question that I asked, which was that, you know, the Berenson, Mayo, or UANS approach?

Dr. Orlowski : Sure. Well, as you pointed out, there are a number of different ways to measure whether a patient's myeloma falls into the standard risk or high-risk category and some people also define an intermediate-risk category and we really do need to do more studies to try to find out which one of these approaches is the best or whether they need to be combined in some way. The FISH, of course, is most widely available because it can be done on the marrow and is part of the standard of care, but I did mention earlier that the gene expression profiling is now available and is paid for by Medicare and many insurance companies as well and so usually I would recommend doing all of these tests if possible, including the FISH and the gene array test, because in some patients they show similar findings and in others they can be complementary and all of these can really help. The big question you have asked, which is most important, is do we treat differently based on the level of risk that has been determined for each patient and this is something we are just beginning to explore. I mentioned earlier that the cooperative groups are doing different treatment approaches for standard risk and for high-risk disease in the newly diagnosed setting where for standard risk, where patients already do very well, we are comparing two different three-drug regimens, whereas for the high-risk approach we are comparing a three-drug to a four-drug regimen and hopefully when those are completed and analyzed, we will have a better idea and the folks at Arkansas are also looking at different approaches for standard risk and for high-risk patients, but right now we don't know for sure whether a different treatment is better for one group or another in part the way I use the risk information is especially after transplant because for people who are standard risk and have gotten a transplant, probably maintenance with lenalidomide alone is sufficient, whereas if they have high risk, I feel and many others feel although this hasn't been proven, but there is the thought that perhaps you need both lenalidomide and the proteasome inhibitor like bortezomib and actually we are right now at MD Anderson pioneering a different approach with lenalidomide and the oral proteasome inhibitor we mentioned earlier, ixazomib, and so this is an all-oral maintenance regimen that may be especially of benefit to high-risk patients. You don't have to get an injection but may also be of benefit for standard-risk patients as well.

Gary Petersen : Thank you. Excellent… Excellent answer. Pat, your question? Pat Killingsworth!

Pat Killingsworth : I am here.

Gary Petersen : Your question?

Pat Killingsworth : Just switching from speaker mode… Okay. All right. This reader asks whether smoldering or after treatment if a patient has a low level of M protein, how long can this condition last before the myeloma reactivates? Is it possible that some people have gone through extensive treatment and have low residual M protein, its simply this in an MGUS state that has been undetected in the first place and which might not return to active myeloma, sounds like they want a glimmer of hope, doctor.

Dr. Orlowski : Well, I think there is a lot of hope to be had fortunately. Let's start with the smoldering situation first. There are a number of ways where people with smoldering or, what now is called, asymptomatic myeloma, can be risk stratified which include based on serum free light chain numbers and also monoclonal protein level into patients who are either at high, intermediate, or low risk of progressing to symptomatic myeloma and so if the patients can have their doctor put those numbers together, then they

may be able to get a better idea of what their chances are in general of progression and we know that some people with smoldering myeloma never progress to symptomatic disease and never need any treatment. So, that's encouraging, although we are not yet at the point where we can identify which individual patient will progress and which one will not. As for whether its possible from a myeloma state to go back to a situation where you have a low-level monoclonal protein that doesn't do anything for a long period of time, the answer is very much so. This can happen and we now have a concept in both the upfront and the relapsed setting, that as long as the monoclonal protein that we see is at a relatively low level and there is no evidence of progression or organ damage, that a period of watchful waiting without therapy may be very appropriate and it may be that some of those people have recurrence just of an MGUS-like state and not full blown myeloma.

Pat Killingsworth : Thank you, doctor. Gary, would you want me to pass it on to Jack or do the next question?

Gary Petersen : Yes. Yes.

Pat Killingsworth : I got it, Gary. I have got it. Doctor, we have a couple of IgD, "d" as in dog, myeloma patients in our support group and others have asked as well. Is it true that IgD myeloma is considered more aggressive and does it have different survival rates for IgD patients that go through stem cell transplants? Do the rates differ meaningfully from IgA and IgG and is there anything more a patient should do with IgD? Is it inherently more aggressive on its own even if the patient doesn't necessarily have other high risk factors?

Dr. Orlowski : Well, its a great question and for those of the listeners who maybe don't know about IgD, as in dog, myeloma, you can have IgG, as in good, although its not good, of course, but "g" as in good, myeloma. You can have IgA myeloma. You can have IgM. Some people feel, "m" like mother, myeloma, although there is some controversy about that. Many people feel that IgM is seen predominantly just in Waldenstrom and, of course, you can have light chain multiple myeloma. Sometimes IgD myeloma is under recognized because every patient who has light chain myeloma should also be tested just to see if IgD is present or not. There is some controversy in the field about IgD, as in dog, myeloma. Part of it is that the number of these patients is usually relatively small, which makes it difficult to try to compare different studies because most clinical trials will have a very low number of these patients and its tough to make firm conclusion. Some studies do suggest that IgD myeloma is more aggressive but others don't and suggest that the outcomes especially with induction therapy and transplant can be roughly the same as in other types of myeloma and what probably is most important is not so much the subtype of myeloma but some of the other factors that we have mentioned before, like the gene expression profile as well as the FISH and maybe also the International Staging System Stage. Those are probably more likely to be of influence on outcome than anything else.

Pat Killingsworth : Thank you. On to you Nick or Priya!

Priya : Yes. We have about 6 to 7 minutes and we can try and get one or two questions from our listeners. Listeners, you may press 1 on your keypad if you have a question for Dr. Orlowski and we will bring you live on air to ask your question. (Pause) Listeners may please press 1 on your keypad if you have a question for Dr. Orlowski. I think, Jack, you can go ahead with your question.

Nick Van Dyk : So, I… Normally we don't have real individual particular questions here, but I am going to break that rule because it frankly applies to me and I am interested. (Laughter) Okay. I did tandem transplants under Barlogie with three years of VRD and I have got lingering GI issues, so much so that at age 44 I am getting an endoscopy tomorrow. So, I am wondering have you noticed a lot of long-term damage to intestinal tract from melphalan and extensive maintenance or am I just a special case?

Dr. Orlowski : Well, first of all, good luck with your endoscopy tomorrow.

Nick Van Dyk : Its going to be a little slice to have and I can't wait.

(Laughter)

Dr. Orlowski : Well, look at the bright side. It will be a lot better afterwards.

Nick Van Dyk : Exactly.

Dr. Orlowski : Yeah. You are raising a good question. We do know that unfortunately some of the therapies that we use, including bortezomib and to some extent lenalidomide can have GI effects and you also probably are aware that some folks unfortunately with myeloma can develop amyloidosis, where you get deposition of the light chain in particular, although other proteins in some cases in areas of the body which can include the gut and that can damage the nerve in the local area and therefore cause problems in things like moving food and other things through the GI tract. So, hopefully, when they do the endoscopy, they won't find anything such as infections or erosions or ulcers or evidence of amyloidosis, but those will be some of the things that would be considered possible and it depends a little bit on what symptoms you have, but those will be some of my concerns moving forward. Hopefully, you won't have any of them.

Nick Van Dyk : Thank you.

Priya : Yes. We have a question from one of our listeners. Person calling in from 805985, please ask your question. (Pause) The caller from 805985, you are on air. Please ask your question.

Caller 1 : Can you hear me okay?

Dr. Orlowski : Yes, go ahead.

Priya : Yes. Yes. We can hear you.

Caller 1 : The question is the patient that received a stem cell transplant in November and is currently on Revlimid maintenance following is having the side effects of a body rash, and, Is there a danger to continuing Revlimid with the rash or is that something that could just be worked through to see if it subsides?

Dr. Orlowski : Yes. Good question because rash is one of the most common side effects for lenalidomide and what I typically do in these settings is I hold the lenalidomide until the rash resolves and then I restart at a lower dose and most of the time what I find is that patients then don't have a recurrence of that rash and in most of the cases, I am able to go back up to the original dose that was used at the beginning and the rash typically does not recur. The concern with the rash is that in an occasional patient the rash can be significant and lead to skin damage, which of course can cause problems in terms of infection. So, I usually do try the approach I mentioned, rather than to try to push on through. Now, if you tell me that the rash is only in one small patch and is not really much of a problem, I might push on through, but if its a more generalized rash, I would probably try to stop and then restart once its gone away with a lower dose.

Caller 1 : Yeah. Its pretty (unclear audio) now and his dosage is actually 15 mg. So, there is some room to step down.

Dr. Orlowski : Sure.

Caller 1 : Another question about what's, you know, the recommended maintenance dosage is (unclear audio) tolerable or do you stick with the standard, you know, 5 mg dose?

Dr. Orlowski : Well, the cancer and leukemia group study that was done in the US which established in part along with the French study, lenalidomide maintenance as a standard began with 10 mg of lenalidomide which was taken everyday and then after three months the dose, if it was tolerated, was increased to 15, but it would not push past 15 mg. So, in general for maintenance, the goal is not to push it all the way to the highest tolerable dose but to try to find the dose that the patient will tolerate, hopefully for years and years

because that means that the myeloma is staying away.

[01:00:05] Terrific! Thank you so much.

Dr. Orlowski : My pleasure.

Priya : I think… Yeah. Gentleman, we are almost coming to the end of our time and today answered over 8 questions out of the 11 that we had. Great going! Dr. Orlowski, thank you very much. It was an honor to have you here today. Gary, Pat, Jack, and Nick, thank you very, very much. Cure Talk thanks all its listeners and participants. Thank you all for your support and we look forward to having all of you join us for the next Cure Panel Talk Show. Fore more details of upcoming shows, please visit trialx.com/curetalk. Thank you.

Nick Van Dyk : Thank you, doctor.

Dr. Orlowski : My pleasure. Take care, everyone.