Improving Practice and Future Perspectives: Panel Discussion

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Dr. Orlowski: As the moderator, what I am going to do is, I am going to answer the easy questions and give the hard ones to the panel. I am going to give all of them to the panel. So, this one is to Dr. Voorhees. A 62-year-old male, who is diagnosed with IgG kappa myeloma, gets 4 cycles of VRd, and the protein normalizes, but a repeat bone marrow shows that there are still 70% plasma cells versus 90% at the time of diagnosis. So a nice M-protein reduction, but not much in the way of reduction in bone marrow involvement. What would you recommend at this point? And Dr. Nooka could opine as well, because this is an interesting question, it does come up every now and then, and it is one reason why it is important to repeat a bone marrow before, for example, you go and do stem cell collection.

Dr. Voorhees: Yes. So, the first thing I would say is make sure that you are monitoring the patient with serum-free light chain testing in addition to SPEP serum immunofixation testing because this is someone who may have had an intact immunoglobulin at diagnosis, but may be developing free light chain escape that you would miss if you are not monitoring serial serum-free light chain testing as well. If the patient has normal serum-free light chains, no M-spike, and they have this burden of disease in their bone marrow, then they technically have nonsecretory myeloma at this point, and they have what we would consider refractory disease, they really had no meaningful response to VRd therapy. So, this is someone that I would consider for a non-cross-resistant regimen such as pomalidomide-daratumumab-dexamethasone or carfilzomib-pomalidomide-dexamethasone in this particular case given that they are resistant to bortezomib. Carfilzomib has activity and bortezomib-resistant disease, but it is not quite as robust as it is in bortezomib-naïve or -sensitive disease, so I would probably lean towards the DARA-POM-DEX in this particular case.

Dr. Nooka: I agree. So, basically, it is either nonsecretory, or if you look at the entire hematological profile, say you do not have a complete 70% plasma cell involvement without any changes in the hematological profile, so you would be seeing other subtle suggestions about the

hemoglobin and so on. Those all should be taken into consideration, and more importantly, the free light chains certainly can help with what you are saying, and clearly, to me, unless proven otherwise, this looks like a primary refractory disease.

Dr. Orlowski: Which fortunately does not happen much anymore, but is a problem when it does. This one is for you, Dr. Nooka. Can you re-challenge a patient with bortezomib once blepharitis resolves, or do you just give them doxycycline and continue the bortezomib?

Dr. Nooka: Yes, we can re-challenge. I certainly will hold off. Typically, these are seen mostly in the induction treatment. I had one patient that we even saw in the CASTOR trial who previously never had any problems with this, which changed my complete opinion that yes you can see at a later time too. But the majority of the times when you are seeing in the induction setting, you are already getting a 3-drug regimen. I am holding off on bortezomib when this happens. When the blepharitis resolves with topicals and the doxycycline, I restart them back again, but I continue them on doxycycline and suppressive therapy for a long time, even to the point of few months, 3-4 months.

Dr. Orlowski: Okay, this will be a question for both of you, which is another good scenario. Do you approach patients with significant extramedullary plasma cytomas differently in the relapsed/refractory setting (its development of several plasmacytomas on what looks like KRD), extramedullary disease, multiple plasmacytomas, as we all know a difficult type of patient to try to treat?

Dr. Voorhees: Right. This is obviously a high-risk patient by virtue of the extramedullary disease, and just as importantly the fact that they are progressing on KRD therapy. So, unfortunately, the numbers of patients with extramedullary disease that are enrolled in clinical trials is relatively low, typically 10% at most, oftentimes it is not rigorously assessed in the lead-up to the study. Oftentimes, bone surveys are all that is required to go on, unless there is clinical suspicion of extramedullary disease. So, in this particular case again, I would move towards a non-cross-resistant regimen, and again, daratumumab-pomalidomide-dexamethasone would probably be my preferred choice in this particular situation. Daratumumab monotherapy did have a similar response rate in extramedullary disease in the phase II studies as it did in non-extramedullary disease, so I think that that would be a perfectly reasonable regime in this particular case.

Dr. Nooka: I agree with that. So, usually the extramedullary disease, the mainstay of treatment is a proteasome inhibitor-based backbone is what I used to rely on, so if he is progressing on the most potent proteasome inhibitor, I think certainly going on with an antibody combination with something that he has not seen as a combination is what I would go with. DARA-POM-DEX would be my choice too.

Dr. Orlowski: And some kind of high-dose therapy could be considered as well. Usually, these folks do not stay in remission on standard-dose chemotherapy for very long, even though if you can achieve the remission, so I think you need to think about some kind of, whether it be transplant or radiation as a consolidation, some other therapy. These are high-risk patients who do not stay in a low disease state for long.

Dr. Voorhees: Absolutely.

Dr. Orlowski: Now, a couple of questions on this card. First, would you ever give carfilzomib at 56 mg/m^2 outside of a clinical trial?

Dr. Voorhees: So, the answer is yes. You know, that is the ENDEAVOR dose that was used. 56 mg/m^2 on days 1, 2, 8, 9, 15, and 16. That said, you do have to be careful about the patients in whom you would use this kind of dosing, and you would certainly would want to infuse the carfilzomib over a 30-minute period in that particular context. If someone has very poorly controlled hypertension, if they have got congestive heart failure, if they have significant renal dysfunction, those sorts of things, you would want to certainly proceed very cautiously under those circumstances, but yes, I do use that.

Dr. Orlowski: I am assuming you do the 20 mg on day 1 and 2 of cycle 1.

Dr. Voorhees: Yes. So, we do the step-up dosing, so 20 mg/m^2 on days 1 and 2 on cycle 1 and if they have tolerated that, go up to the higher dose, and I do not use 56 mg/m^2 in that dosing schedule with triplet therapies.

Dr. Orlowski: So, Dr. Nooka, we will shoot this one to you. It says here, almost all written VRD regimens described 1, 4, 8, 11 IV bortezomib, but most people seem to do subcutaneous (subQ) weekly bortezomib, so which do you recommend with the VRD regimen?

Dr. Nooka: So, with VRD regimen, it is IV to subQ. We do subQ 1, 4, 8, and 11 in the induction setting. So, that is a standard. If it is 3-week cycle that you are talking about, it is 1, 4, 8, 11 subQ with lenalidomide given 1 to 14 with a 7-day break and dexamethasone given 20 mg on and after the day of bortezomib, and I would go with the dose reductions on bortezomib. So, this is the original paper that was published by Paul Richardson in *Blood* 2010. The only changes that we are making is changing the IV to subQ, and that has been our standard, and with this regimen, we are seeing VGPR rates of close to 70% after the first 4 cycles with less neuropathy that is close to 6% grade III peripheral neuropathy.

Dr. Voorhees: I will just say in some older patients what I do is 4-week cycle where I will do the 3 weeks on, 1 week off of lenalidomide, and I will do the bortezomib subQ once per week, because there is, as you mentioned, less neuropathy with the once per week. So, I think the twice-weekly is probably better for younger more robust patients.

Dr. Nooka: Certainly. I think it was RVd-like treatment that basically going on with once weekly.

Dr. Orlowski: So, Dr. Voorhees, we will shoot this one your way. Any cardiac findings that are absolute contraindications for carfilzomib?

Dr. Voorhees: That is a tough question. I do not know that we actually know the answer to that very well at this point. I think there is a lot of additional study that needs to be done. I have generally steered away from carfilzomib for those patients that have systolic congestive heart failure, so if their ejection fractions are less than 40%, I have generally steered clear of it, but there have been certainly situations where I have exhausted my other options, and I have cautiously proceeded, usually with the handholding of a cardio-oncologist with carfilzomib in

those situations. I am certainly more comfortable with it if their EF is low, but they are relatively asymptomatic.

Dr. Orlowski: Dr. Nooka, this is for you. Do you see less cardiotoxicity with carfilzomib when it is given at a 70 mg/m^2 dose once weekly?

Dr. Nooka: That was a tough question. That was the dosing based on the CHAMPION trial. My personal opinion, I have never given 70 mg. I always, if I am using it as a doublet, I cap it off at 56 mg/m^2. If I am using it in combination with other agents, I cap it off at 45. So, in 70 mg, theoretically, you are getting once-a week-dosing almost equivalent to what you are getting as a twice-weekly dosing. There is no reason to believe otherwise, but I do not have the right answer.

Dr. Orlowski: Although, there are some randomized studies that are being done to compare carfilzomib given once-weekly at the higher dose with the standard, I would say, I guess, intermediate dose, carfilzomib given twice-weekly. So, hopefully, we will have more data. This is for Dr. Voorhees, although it really could apply to all of us. Can you clarify how you define LEN or VEL refractory since we know, for example, that patients treated with RD will still response to KRD even though they have progressed on lenalidomide? So, essentially, how do we know when it is no longer useful to treat with lenalidomide?

Dr. Voorhees: Right. So, I would argue in that case, it is possibly the KD that was exclusively responsible for the response in that particular patient. We talk a lot about synergy of these agents, although it is very difficult to prove clinically, it is much easier to prove in the laboratory. What I would say is there are relative degrees of resistance. I would say that progression on maintenance doses of drug would be kind of on the low end of spectrum of resistance, but if somebody with normal renal function is progressing on a 25 mg dose of lenalidomide and a once-weekly dose of DEX, they are LEN-DEX refractory by definition, and yes, you can add K in that situation and they may have a nice response to therapy, but that does not necessarily mean that the LEN-DEX had anything to do with it. In that particular situation, I would probably switch to something other than LEN-DEX as the carfilzomib partner.

Dr. Nooka: I think I completely agree with that. None of the patients on the ASPIRE trial were progressing on lenalidomide-dexamethasone, then they went on, so we do not have data to back that. The patients who were progressing on LEN-DEX were the ones who would have a response with KRD. If there is response to me, theoretically, it probably is the ENDEAVOR KND that is giving the response.

Dr. Orlowski: I mean, ideally, what you would need is a trial where you take people progressing on RD and you do a randomization to either KD or KRD and see which group does better, and then you would have some idea of whether adding the R is still of benefit, but given all the new drugs we have all out there which probably will have better activity, that question I would not say is the top one on people's list, unfortunately, to progress. The other thing is, of course, some years ago, there were data about cereblon as the target for the immunomodulatory drugs and that if you did not have cereblon expression, you probably should not be getting either THAL, or LEN, or POM, but now things get even more complicated because that may be different with antibodies because if the myeloma cells do not express cereblon, it may be that their impact on the immune cells in the microenvironment in combination with the antibody will be enough that it

does not matter whether the myeloma cells express cereblon or not, even if we had a validated assay to measure it, which we unfortunately do not. And then, here is the last question, which is also going to be a little bit challenging. How does post-transplant relapse affect your choice of therapy?

Dr. Voorhees: So, I think it is going to dependent on what maintenance therapy that they are on at the time that they relapse, and the timing of the relapse with regards to its proximity to the transplant and the pace of that progression. So if you have a patient who is on lenalidomide maintenance therapy and is progressing 12 months after their stem cell transplant, whether they had high-risk disease biology at baseline or not, that is someone who is falling outside of the expected course in a patient such as that, and I would consider that high-risk disease, and I would typical treat that patient with a triplet. And, in that case, just as an example, bortezomib-daratumumab-DEX would be a good level 1 evidence triplet, but you would have several choices to use in that particular circumstances. So, it really depends on what they are on and the timing from transplant.

Dr. Nooka: There are three factors that are taken into consideration. The first one is, again, the pace of the response, the slow response or aggressive response. The second one is, whether they are in LEN maintenance or no LEN maintenance. If the patient has a slow progression who did not receive any lenalidomide-based regimens, probably those are the ones that I certainly think that can benefit from these subtle regimens like elotuzumab-LEN-DEX or the ixazomib-LEN-DEX, where you have the liberty of giving them a regimen that is more convenient for them. Whereas, if the patient has aggressive relapse or high-risk features of their relapsing, certainly this buys in for a three-drug regimen, there is no doubt about it, that is when I will be very aggressive with either a KRD regimen or KPD regimen. If they are on LEN maintenance, I would go with KPD; if they are not on LEN maintenance, I would go with KRD, and using other CASTOR trial with daratumumab-bortezomib-dexamethasone, something that the patient has not been on, a non-lenalidomide based approach with a third agent is what I would prefer in an aggressive agent other than ixazomib and elotuzumab.

Dr. Orlowski: And also, it is worth to do a reevaluation of the patient at the time that they relapse because even if they had “good-risk disease” at baseline, even if they relapsed two years out, that does not necessarily mean that they may not relapse with high-risk disease, and that may inform what you decide to do because if they relapse with high-risk disease, then clearly a triplet would be preferred if possible rather than a doublet for some of the reasons that you have heard.

Those were all the questions. I do not know if you have other cases that you wanted to mention, and if not, thank you all for. Oh, I am sorry, we do have one question. Please, there is a microphone right behind you.

Question from audience: **Who are the patients that you referred for CAR T-cell?**

Dr. Voorhees: So, I would say that those patients who have certainly, what we call, quad-refractory patients, so the lenalidomide, bortezomib, pomalidomide, carfilzomib-refractory patients, certainly would be wonderful candidates. We are certainly seeing a lot more of, what we call, penta-refractory disease, which includes those four agents as well as daratumumab. Those patients would be terrific candidates for CAR T-cell therapy as well, and I think we will

see more and more of those patients as DARA gets moved earlier and earlier in the course of the disease treatment course, so quad- and penta-refractory patients for sure. And as we finesse the administration of CAR T-cell therapy and the side effects that can potentially come with it, the CRS, the neurologic complications, we can start moving it into earlier lines of therapy.

Dr. Nooka: I agree with Peter. Basically, with different constructs that you have, you need to have phase I trials at different settings for each of these cards. So, when we are talking about these refractory patients in phase I trials, usually you give them to those patients who do not have a lot of options available, so probably, I think those are the patient who were penta-refractory or quad-refractory who are eligible for phase I clinical trials, so as the ones where their safety is proven, then if it is safe mechanism, safe construct, then you move towards early lines of therapy, and maybe one day, in the newly diagnosed settling, somebody will have it like Oprah said.

Dr. Orlowski: And the main things to remember also is to look up the inclusion and exclusion criteria, for example on *Clinicaltrials.gov*, most of the CAR T-cell studies that I know off in myeloma right now exclude people who had prior allogeneic transplant, so that is something to know about. Also, because of the manufacturing time, if it is an autologous T-cell product, these are folks that should probably not have explosive disease, because you are going to have to get the disease under some control, you are going to have to phorese them, it is going to take probably 2-3 weeks for you to get the product back. Most of the studies do allow some kind of therapy in-between to temporize, but if they have got very high-risk disease that is just exploding on you, for example, plasma cell leukemia which is also usually excluded just because of the concern for a higher risk for CRS. I think even though our tendency is that we want to get those higher-risk patients on, I think, unfortunately, functionally, it is going to be more difficult because of the timing involved. It is not like you can sign them up for the trial and get started next week yet, unfortunately. There are some studies that are going to be starting, for example, probably next year at MD Anderson with an allogeneic T-cell product, and the advantage there is that it is off-the-shelf, so you do not have to phorese the patient, send the cells off, manufacture them by infecting with a lengthy virus or whatever, expand them, and so forth. It is an off-the-shelf product, but there is also then the risk of GVH and other complications, so those are some considerations as well.

Alright, well, thank you all for staying late, and I hope you enjoy the rest of your stay in Chicago, and thanks very much for participating in this event.