Managing Myeloma

When First-Line Treatment Fails:
Navigating New Treatment Paradigms in Relapsed/Refractory Multiple Myeloma

Module 3

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Dr. Andrzej Jakubowiak: So, now real life, something which I will try together with Dr. McCarthy, discuss with you how we can integrate some of these pieces of information you have learned from him and what I discussed today into a few cases which we present here. The first case is a 67-year-old man who presents with IgA- predominant myeloma stage 1 International Staging System, and no high-risk feature. He received induction with bortezomib/dex, two drugs, which was popular on NCCN Guidelines not long ago, but at about the third cycle or so, or maybe second, he is appearing like he is progressing. What would you assess in this patient for relapse? Some questions which we ask you to answer at this point coming from the definitions which we showed you earlier and Dr. McCarthy, you remember CRAB criteria and some biochemical relapses, and you have measure change of serum creatine and calcium, beta 2 and LDH, MRI or other imaging like PET not included here, another repeat of FISH at this time, or measure M-protein or free light chains. M-protein means myeloma protein. I am going to show you what you are thinking. So, most of you would order FISH, and responses are coming. Measure of change of serum calcium and creatinine is appropriate based on the clinical relapse which is the CRAB criteria mostly. I am actually surprised no one has been measuring myeloma protein, I think that is what we actually mostly do, and I think that is something what I would recommend that we continue to use, especially nowadays, in our practice. Dr. McCarthy, you may have overlooked, it but I want to stress his point which he made. He had said earlier that in newly diagnosed patients, and it is now entering into the patients who are relapsed, we previously were not moving with treatment until there was emergence, imminent, or already emerging organ damage, which was the definition of CRAB criteria. We added new criteria for newly diagnosed patients, significance of involvement of bone marrow, free light changes, and MRI changes. These essentially put patients earlier into the treatment and the emphasizes the last couple of years to 3 years is that we want maybe not to rush to treat patients too early, but at the same time not necessarily wait until organ is actually being damaged. So, there is a balance here to change, and I think from that perspective I would stress actually at this meeting that monitoring patient's myeloma, monoclonal protein, and free light may help you out. You do not have to jump to the conclusion that you start treatment at that time, but you need to know that the patient is progressing or not.

Dr. Philip McCarthy: One thing up here is I would not be looking at the measure of change of beta-2 microglobulin. Nobody does that, but if you checked it at all, that is not a good idea. I mean we could argue the fine points of the electronic system; however, number 2 should not have been checked. Number one could have been checked, the last one. The FISH, I would not do either unless I saw that something was wrong with 1 or the last one, and I would get an MRI if the patient had bone pain. So, that is sort of to give you a feel.

Dr. Andrzej Jakubowiak: I completely agree with you and that is my commentary with you, and regardless whether we designed the slide well or not and what were the choices, I think this was stimulation for us to think what we should be doing, and I agree with you, Phil, that at this point we probably know earlier in 90 plus percent of cases which we monitor carefully the patient is progressing or not by measuring M-protein. If the patient dropped from the clinic, traveled, or something bad happened, sudden transformation of the disease, you may end up discovering that creatinine or calcium went up, that is possible, but I want to also stress that I would perform some imaging in this patient, especially if there are symptoms because I had had patients who had not had any change of myeloma protein but had developed focal progression of the disease and sometimes it is a bad sign of transformation of the disease or worse in the case of disease behaving. I want to remind you of two slides which Dr. McCarthy reviewed with you, that for defining relapse disease clinically we look for rise of creatinine to 2 or higher, calcium to those levels shown here, development of new soft tissue, or definite increase of bone plasmacytomas and by more than 2 g decrease of hemoglobin related to myeloma. So, if you have those findings, that is clinical relapse and that has been defined about 10 years ago as you can see in this paper, but we are also looking at increases of myeloma protein. More than 25% is required, and it is shown here also that 25% must be also by more than 0.5 or 5000 mg/dL of myeloma protein. We also started developing evaluation of measurable disease by light chains only. Here, for 24 hour urine, 200 mg is a minimum increase, also by 25%, but when we are looking for free light chains, many of us are sometimes I would say even confused because free light disease is usually an earlier sign of progression, and sometimes if there is a light chain escape, it may be the only sign of progression. We actually are trying to stress that for patients who have heavy chain disease, like for example, IgG kappa, that has increased by say 0.2 to 0.4, free light by more than 10, I probably would not call it yet progression. You have to wait until M-protein is over 0.5 for the patient who was in complete response, but these are more kind of a subtle and granular aspects of relapse and that is what we define. I think it is one way or the other important that we define patients who relapse. So, either any of those findings or more than 25% and 500 mg, more than 200 mg in 24-hour urine or free light, but also rapid relapses with CRAB symptoms. Doubling time may be not necessary, yet reaching criteria about if you see that it is going so quickly or early relapse after transplant, especially within 1 year. These are the patients who are those rapid progressors and we need to put them on either. You want to say something?

Dr. Philip McCarthy: I completely agree, and the idea now is that when we see these sort of low-grade relapses, you cannot say, “Well, come back and see me in 6 months.” It is not a good idea. You want to make sure they are being followed, and the ones who are developing symptoms, you are going to get them treated, but it is really important because sometimes I have seen patients who come in, I have not had their monoclonal proteins tested in 6, 9, and 12 months, and that sometimes makes me very nervous because you could miss something and then all of a sudden you have a patient who now has end-organ damage and it might have been prevented.

Dr. Andrzej Jakubowiak: And I mentioned where you have heard the phrase light chain disease. Sometimes, in some practices, 24-hour urine, we all know is a nuisance. Patients hate it. We do not like it. Not all pathology labs do a good job with measuring that. You cannot interpret what is there. So, free light helped us, but I want to say that there is sometimes discordance between free light and 24-hour urine. I would periodically recommend gold standard of care to check for light chain disease. You may have IgG stable, nothing is

happening, but you may have really emergence of critical and dangerous relapse because light chains can kill function of the kidneys. So, what happened with this patient after all your evaluations which you just did? So, this patient had increase of creatinine modest from 1.2 to 1.4, hemoglobin decreased from 12 to 9.6, by more than 2 g. There was a PET scan done which showed that there is increase of one of the lesions from 0.5 to 3.5. There was also increase of M-spike IgA kappa from 1.6 to 2.4. Sometimes, it is tricky for IgA, but that is what they say here, and at that point, you can say with confidence this patient relapsed. What treatment option we should chose for this patient next? These are your choices now.

Most of you would use for this patient carfilzomib/lenalidomide/ dexamethasone. Now, it is changing to ixazomib/lenalidomide/dex, also triplets. There is also triplet, elotuzumab/ lenalidomide/dex, but it looks like it would be less popular. I agree that daratumumab nowadays probably most of us would not get approval yet to use it. So, even if many of us would probably like to use it, I do not think we could, so what do you think about the choices?

Dr. Philip McCarthy: Yes, I think that is reasonable. I think if you have got somebody who is rapidly progressing, then I am thinking of carfilzomib based. If it is less so, then ixa or elo. I think elo, especially if it is slow, and again, it is for the first. These all can be used as first options, and as you say, dara monotherapy, and really I would not be thinking monotherapy anyways based on the CASTOR and POLLUX data, looking more at combinations.

Dr. Andrzej Jakubowiak: So, here, you have seen those slides, and there are really to remind us how many choices we have, and this is a reminder that we have slow-relapsing algorithm, and I would like to say that we academicians always would say, not everybody would agree with that in general practice, but if we have so many choices, we do not know what to do, let's learn from this and potentially consider enrollment of patients in a clinical trial. I think it makes my life easier. I do not have as many headaches because I have one top trial which is enrolling patients in any given category and that is what makes my life easier, I am not thinking why this or not the other one. But here are the choices and what gives us some guidance. We can take IMiD-based regimens for patients. If there was no underlying peripheral neuropathy, there was no prior IMiD exposure or there was a good response to IMiDs before, and there was prior IMiD use, you sort of have this patient like that. Then you have patients who are lenalidomide-naïve like this patient, and you have here choices for patients who are lenalidomide-naïve. But having relapse or bortezomib refractory like this patient, you still have some choices which are listed here including carfilzomib/lenalidomide/dex or daratumumab/lenalidomide/dex which is emerging and I am sure will be coming into the space, and elo/len/dex. Here are PI-based regimens. This is a patient progressing, remind you, on bortezomib/dex. We usually pick them up if the patient was on prior IMiD. We switch classes or at least at a new class. Those who are known previously exposed to proteasome inhibitor, or those who had prior proteasome inhibitor but had tolerated it well and had good durable response, and we definitely want to pick up proteasome inhibitor if there is 4;14 translocation. And then we have, again, two categories in this group of treatment was PI based. Bortezomib-naïve, which was not this patient or lenalidomide refractory, also not this choice, I will get back to them. We also have to remember that this patient has not gotten yet his transplant and transplant should be considered. So, in a way, our thinking should be here probably along with the lines, "Okay, let's reduce this patient successfully and possibly move to transplant." That is my first thinking, but is this slow indolent relapse? How would we think about this patient? Remember, progression after 45 days and with some clinical findings. So, is this patient falling into rapid symptomatic relapse and/or second relapse? Again, I want to

remind you about clinical trials, but if not, we have those choices. I think you have seen Dr. McCarthy and myself, we are less and less inclined to go into traditional chemotherapy, but we still sometimes have to, I have to say, resort to especially VDT-PACE or something of this kind. We have IMiD-based regimens which are listed here, and again transplant. I am not going to spend too much time on it because you already have seen all of these choices. In general, I want to say that in this rapid progressing disease we want to get the patient on as good a treatment as possible, and let's discuss what we can do for this patient. Here are our or experts' discussion points which we would like to bring in the context of this trial. Some of them we already discussed. This patient has primary refractory disease per definition which you have heard from Dr. McCarthy. This patient we can say now, maybe a couple of years ago we would not have said that, had been probably suboptimal and treated. You have at least two or three studies where triplets were better than VD. So, why are we giving patients two drugs? We know that the response will be probably in about up to 60+% to 70% rate. We now have regimens which can have 100% rate, RVD, KRD. Why not to use them, is this something which we have to take into account? We have to also take into account that the patient has symptomatic relapse as evidenced by anemia and the development of those increasing lesions, and I want to ask a question maybe to Phil, Dr. McCarthy. What do you think this patient represents? Slow relapse? It is first relapse, which by definition in this context of this paper was considered sort of slow relapse because it is first relapse, or aggressive relapse?

Dr. Philip McCarthy: I think this is aggressive as this is occurring early on.

Dr. Andrzej Jakubowiak: I think I would agree with that, early on I mean you may not have great responses to bortezomib/dex but progressing with increasing plasmacytoma. In this case, we would recommend, and I think most of us would agree, IMiD-based salvage treatment. So, we have only proteosome inhibitor and dex, but what choices should we take? We have essentially triplets like elo/RD/bortezomib, or RVD, ixazomib/RD or oral KRD or, once assuming that this will be approved in few months, dara/RD. What would be your choice if you would have all of these choices for this patient, Phil?

Dr. Philip McCarthy: I would be tempted to think about dara/RD, but I am thinking based on upfront data now, KRD. I think you really got to hit them hard because this patient is progressing too fast.

Dr. Andrzej Jakubowiak: With KRD, you make two choices which is sort of my one proof of principle which I am trying to apply. If I am changing therapy empirically based on what I know from the data, I am trying to make at least two choices if I can, and in this case, we are adding lenalidomide and we are also switching from bortezomib, the same class of drug, to carfilzomib, which we know is more potent. So, in a way theoretically, at least we are providing this patient a better chance of responding. RVD would not have been a bad choice, and many of us would have done it, probably even now are doing it. It would not be my first choice but that may be based on my experience with KRD which is just showing me that this is a regimen which is going to work and is just going to be for sure giving this patient a chance of getting to transplant.

So, now, case #2, and I want to say that this is a little bit different patient, 56, younger who was initially diagnosed with pancytopenia and hypercellularity. There was 4;14 translocation. She was treated with VTD appropriately and then transplant, probably in a European setting or maybe here, and then went on lenalidomide maintenance, very modern and good treatment

nowadays, I would say. But the disease progressed after 1 year, so relatively early after transplant, but on maintenance of lenalidomide. The patient was then treated with RD, sort of rescue. Many of us have done this. “Oh, it’s too low dose of lenalidomide. Let’s move it higher,” and with dex but responded but relapsed after an additional 8 months. What treatment option would you choose after her second relapse? Here are the choices. You can maybe plug in what you would do. Carfilzomib/dex, elotuzumab/lenalidomide/dex, ixazomib/lenalidomide/dex, and pomalidomide/low-dose dex. Let me show you what you are thinking. It looks like many of you are at this stage looking for elotuzumab/ixazomib based combination. Now, it is more carfilzomib/dex. No one has chosen pomalidomide/low-dose dex. What do you think, Phil?

Dr. Philip McCarthy: My concern, you might have lost the elo window because this patient has progressed on RD, but the len does potentiate the action of elo. So, if you watch the patient very carefully, if it is not too fast, if the pace of the relapse does not pickup, that would be okay. I think carfilzomib/dex is very reasonable. Probably, I want to combine it with something because even though the patient has seen an IMiD, you potentiate the activity of the carfilzomib by adding if you can get away with it. Ixa is another reasonable choice, it might be a little bit slower than with the carfilzomib, so again, slower-relapse ixa, faster-relapse carfilzomib. Surprisingly, nobody picked pom/dex because it is second relapse.

Dr. Andrzej Jakubowiak: It is per label, even approved what we would potentially consider.

Dr. Philip McCarthy: Yes, and you could use it for len refractory because you often will salvage, but I think it is a reasonable option, at least within the context of how we explained it.

Dr. Andrzej Jakubowiak: I think all of them are reasonable choices, it makes our life more difficult, but at the same time the commentary you hear, and I will also make mine, helps you know how our thinking is and potentially you can guide yourself. So, I think in this particular context, again using the same principle which I told you earlier to make two choices, the patient is progressing on RD now and have been previously sensitive to proteasome inhibitors. I think that to make two choices I probably would like to use pom, and I probably would use a triplet, and why use triplet? It can be pom/bortezomib/dex which has been not yet evaluated in a randomized setting, or presented at ASCO at oral session KPD regimen, carfilzomib or carfilzomib/pomalidomide/dex, that gives you two new drugs and not previously seen high responses, very good durability of responses, and that empirically may not work but has probably over 80% probability of achieving response and quite durable response, and probably some superiority over other potential choices here. They are all reasonable. I want to stress that we truly do not know which of these choices is better because those regimens were not compared side to side. I think carfilzomib/dex alone is not a bad choice, previously sensitive to bortezomib therapy based. Again, no one would know whether it would work better. Why not throw in pomalidomide on top of it, right? So, here again sequencing, this time, we all agree this is second relapse, rapid relapse, choices on the left for chemotherapy, in the middle IMiD or PI based which are listed here, and auto transplant. I think in this case I would say that we probably should focus on PI-based regimen because we have the patient progressing on Rev/dex and it is bortezomib sensitive. So, we probably can pick up any of these choices as reasonable, and we do not have here, and if you add to that lenalidomide-refractory group, which is this patient, we have those choices added KPD here as one of the potential choices. So, I think that this is how the thinking is in the context of this particular patient. And again, some discussion points from us about this particular case, we think this is the case of

intermediate risk with 4;14. We want to keep proteosome inhibitor for this patient. It is probably something I would have done in post-transplant setting knowing 4;14 for extended time which is not standard of care, but as you see the patient is relapsing early, this is at the moment biochemical relapse, but we think that in this particular situation the patient probably will be served by treating the patient with PI-based regimen. We want to stress that while the patient was theoretically sensitive to lenalidomide, because progression of maintenance, lenalidomide was not necessarily considered refractory to lenalidomide. In a later phase, the rescue was normal doses of lenalidomide/dex presumably, and these types of patients were not evaluated actually in any of the randomized trials. These patients were not in the DRD versus RD trial. They were not in ixa/Rd versus RD. They were not in elo/RD. So these options may work, but they were not necessarily tested in this patient population. Ideally, this was outdoors of this slide conclusion, not mine. You would use third-generation of IMiDs. I would agree with that. I mean pom, we discussed that. The third case which is sort of a nice way of wrapping up the things which we discussed today. A fit 74 year-old gentleman who was diagnosed with MGUS initially, so slowly progressing, and then progression of light-chain disease in 2010, eventually was into induction receiving transplant and then received lenalidomide, was long, 3 years in remission, but relapsed. Upon assessment, he was still considered fit. What treatment options do you have for this patient? It does not matter at this point for our case review what was induction, but is was transplant, 74 but fit, and chemical relapse. What would you do of these choices? Ixazomib/lenalidomide/dex is emerging as the primary choice. So, pomalidomide/low-dose dexamethasone is another potential choice for many of you. What would you do? Again, put you in the spot.

Dr. Philip McCarthy: I think these are reasonable. I guess it depends. I would not want to give up on elo because it is the one time where you might be able to get some mileage out of it if it is a slow relapse because this may be your only opportunity to use that, because if you get somebody who is further down the track, which I had mentioned before, I think I like the idea of combination of the ixa/len/dex or car/len/dex. Both of those I think would be good, and again if you want to go fast, you need car/len/dex a little bit. If you got time ixa, pom/low-dose dex would be fine as well. It depends if there is any frailty on the part of the patient. Obviously he is 74, and if he is quite fit, are you even going to think about doing another transplant on him? But I think you want to get control of disease and I think all of these would be reasonable with, again, close monitoring because you want to be able to switch or be thinking, “If this patient is progressing, I want to get a little more aggressive.”

Dr. Andrzej Jakubowiak: Very good and helpful to me in discussion, the way I was thinking at least and then line was my thinking. I would remind myself that this patient had good response to transplant, long lasting, can get very good mileage, is 74, so it is pushing the envelope in this regard, but we transplant 74 year olds if they are fit and have no other problems. If this patient, and you have good fair discussion, feels I am going to go for 100 years, it is good to go for me and I do not want to take any chances. It probably would give you better chance of having longer control of the disease if you have good aggressive reduction of the disease, then transplant and then again some kind of form of good quality of life, and extended maintenance therapy. That has good probability of working well. If the experience with transplant was not good or at some point he concludes or she concludes that, “No, I am not going to do anymore transplant. I am done with that.” Then, I probably would be, in this particular case, relatively slow, even if it is a definite relapse, that may be a quality of life issue, and controlling the disease was extended treatment, something which will not annoy the patient, maybe not a bad

alternative to more aggressive therapy. So, that is how I would potentially approach it, and again, we have seen this slide. This is a fit older, somewhere in this category you can pick up any of this, and I think any of this would be good. It is a good situation that we really do not know what it is. I think one can guide yourself or herself by knowing which regimens give you the biggest mileage, and if the patient is interested in something of this kind, then you will have those choices. And again, some discussion points which I would like to bring in and wrap it up with us. This is a fit gentleman, even if he is older. He did not progress on treatment doses of lenalidomide, he might be considered for lenalidomide sensitive type of therapy. So, any of the choices are reasonable. You may have to remember that age is age. So, do not really overdo it with dexamethasone. You need to lower those doses, and if you have tolerance and issues develop, you have to modify the treatment as much as you can. This is one of the last points in this slide. Do not forget about transplant as a potential choice for this 74-year-old. It is a reasonable point to take in the discussion for treatment.

So, last slide, to summarize and to just give you final points. You have to understand your armamentarium. You need to know that not every patient needs to be treated when they have the chemical relapse. You can observe it for a while if there is a really slow pattern of progression, that probably is okay. I generally do not wait too long. I know that even my best tools may not work. So, I do not want to push it to the limits that organ damage is at risk, but I think the finding the right balance here is appropriate. And then evaluate for symptomatic disease, we need to closely, as Dr. McCarthy has discussed, for end-organ damage. Never hesitate to ask us and our colleagues. That is why we are here for and we are always available. Wherever I work, people know how to reach me and I always will respond. Always evaluate for three important factors, patient related, disease related, and treatment related. And remember, always a balance between efficacy, we can try to develop, we should probably because that prolongs life, but also making sure that we do not hurt the patient, and that the patient can tolerate what we proposed, and that is what we do. Now probably I did not leave too much time, but we have time for questions and answers.