From Quandary to Clarity in Relapsed/Refractory Multiple Myeloma: Optimizing Treatment and Empowering Patients

Activity 2: Therapy for Relapsed/Refractory Multiple Myeloma: Preparing for Novel Agents

Sandy Kurtin: Hello, and welcome to "From Quandary to Clarity in Relapsed/Refractory Multiple Myeloma: Optimizing Treatment and Empowering Patients"—a 3-part educational series for oncology advanced practitioners. I'm Sandy Kurtin, nurse practitioner at the University of Arizona Cancer Center. And I'm joined by my 2 colleagues.

Kevin Brigle: Hi, I'm Kevin Brigle. I'm a nurse practitioner in the hematologic malignancies clinic at the Massey Cancer Center at Virginia Commonwealth University.

Josh Epworth: Hi, I'm Josh Epworth. I'm a nurse practitioner in hematologic malignancies at the University of Washington, Seattle Cancer Care Alliance in Seattle, Washington.

Sandy: In this video, we'll be discussing novel agents for the treatment of relapsed/refractory multiple myeloma.

Sandy: So several important abstracts were reported at the American Society of Clinical Oncology meeting in June of 2019, and also at the American Society of Hematology, or ASH, meeting in December of 2018, specifically relevant to relapsed/refractory multiple myeloma. These have offered some new exciting options for patients, and we're going to talk about a few of these that we think may lead to a change in our practice. So let's start by talking about the CASTOR trial.

Sandy: We know that in the CASTOR trial, they compared daratumumab, bortezomib, and dexamethasone to bortezomib and dexamethasone as a standard of care, and found that there was an improved progression-free survival with a very acceptable tolerability profile or safety signal. They've now gone back to do a subgroup analysis of this study looking at the lines of therapy. So patients who have had greater than or equal to 1 line of therapy and also looking at subdividing standard-risk cytogenetics with high-risk cytogenetics. At a median follow-up of 40 months, there was a statistically significant improvement in progression-free survival across all cytogenetic subgroups. In first relapse and in second relapse there were higher rates of overall response, minimal residual disease negativity, and sustained minimal residual disease, or MRD, negativity in the group getting the daratumumab, bortezomib, and dexamethasone versus bortezomib and dexamethasone alone. So this basically has led us to see daratumumab in a new light, if you will. So talk to me a little bit about that, Kevin, and how this has had an impact on your practice.

Kevin: Well, again, I think this is another triplet which is exciting, exciting triplet. We all know that triplets in every study work better than the doublets. So this has just given us another bullet to use. And so I think the really exciting part about this too is its effectiveness in patients who have high-risk cytogenetics. Those are a particularly difficult group to treat, and we've typically treated them with a proteasome inhibitor and an IMiD. But now we have another thing which we can add to that as well. And it's really encouraging to see that we get MRD negativity in this group of patients, really hard to achieve, and so that really I think we know that MRD is a surrogate marker for progression-free survival, and so that really becomes, I think, a really important addition to the group.

Sandy: And I know we talked a little bit about MRD negativity in video 1 of this series. So let me go to the next study, Josh, and ask you a little bit about this. So this is really looking at giving daratumumab, which we've just talked about adding in a very important monoclonal antibody, anti-CD38 antibody to our options for treatment. And in this study, what they looked at was a noninferiority trial comparing subcutaneous daratumumab with intravenous daratumumab. And really, and this was the COLUMBA trial. And finding that basically there is no difference in efficacy based on pharmacokinetic data. They also talked about a significant reduction in infusion-related reactions and a substantial savings in time where the daratumumab when given subcutaneously required about 5 minutes for the actual administration. And we know that daratumumab in the standard regimens changes incrementally, but ultimately you end up with a 3.5-hour infusion if you're using those standard infusion rates. I know you've had some personal experience with this study; talk to us a little bit about what you think the impact might be in practice with this change in route of therapy.

Josh: Well, daratumumab, as Kevin was mentioning, is a terrific new addition to our tools that we can use against this disease. It has 2 pauses that you get before you initiate it. The first is there is an increased risk of infusion reactions typically over the first 2 infusions of this medication. The second is, it is a prolonged infusion time and as you mentioned, they get shorter, but we're looking at 8 weekly doses, which can be multiple hours stacked on top of each other, which has an impact on the quality of life for the patient.

Josh: But in addition, is a significant burden on the infusion center. The benefit that we see from the subcutaneous version is exactly as you said, we see a lower level of infusion reactions. And in addition to that, we see a significantly shorter period of time that the patient is in the infusion center with no detectable difference – significant difference between the outcomes that we get off of the medication. We are using it right now in my facility in a study with smoldering multiple myeloma; we've seen no significant impacts on their tolerability and no issues on it. I'm really looking forward to when we can use this globally and begin to move away from the infusions.

Sandy: So in the patients who may not want to subcutaneous infusion, it's more than just an injection. Tell me about what you're doing in your practice, Kevin, to minimize those infusion reactions and make that more tolerable.

Kevin: Right? Well, as Josh was saying, the really most significant problems we see are probably in the first 2 infusions. And so we pre-medicate these patients with a standard antihistamine and acetaminophen as well. Also, another agent which we've used is a mast cell stabilizer, which is...

Sandy: Montelukast?

Kevin: Montelukast, correct, yes. And I think the other important thing is patient education. Telling those patients ahead of time what symptoms to expect, these are predominantly upper respiratory tract symptoms where people get congestion with a little difficulty breathing, things like that. And also letting the family know as well, because when they have these infusion reactions, I think it can be, it can be rather – probably a little challenging for not just the patient, but also for the family to watch. And nurses are very good at taking care of these. Advanced practice nurses have managed these infusion reactions for years, and so I think that's probably the big thing. We think about daratumumab and those types of reactions.

Sandy: I know that adding the montelukast has made a huge difference in our practice in reducing the severity of these. We've also adapted the 90-minute infusion based on a small study that was done at Ohio State University, which we introduce after several weeks of therapy. And that has actually also helped with some of the chair time. That is a challenge in any practice where you don't have enough space to treat all the patients that you need to.

Sandy: So now let's shift gears to a different drug, a different class of drugs, the immunomodulatory agents. And specifically, we've talked a lot about the use of lenalidomide and immunomodulatory in the frontline as our triplets in video 1. So let's talk a little bit more about pomalidomide-based regimens. It has been combined with other proteasome inhibitors, it's been combined with anti-CD38 antibody, and more recently, with the SLAMF7 drug, elotuzumab. We know that they're... based on the OPTIMISMM trial, they looked at pomalidomide, bortezomib, and dexamethasone.

Sandy: And again, comparing it to a doublet, so bortezomib-dexamethasone in relapsed/refractory multiple myeloma. And at a medium follow-up of roughly 16 months, the group getting PVd, which we'll call it, was 11.2 months progression-free survival compared to 7 months in the doublet using bortezomib and dexamethasone. And of these 391 patients that were refractory to lenalidomide, we saw a hazard ratio of 0.65, so favoring the PVd arm. We always want to balance efficacy and safety, so looking at the grade 3 or greater adverse events, they were comparable, in some ways, but there was more neutropenia, febrile neutropenia infections in the PVd arm versus the Vd arm. Interestingly, thrombocytopenia was equivalent in that study.

Sandy: The other study that we'll talk about, and then I'm going to get your reaction to this information, was again, combining a monoclonal, in this case, SLAMF7 elotuzumab, looking again at EPd now versus Pd. So elotuzumab-pomalidomide-dexamethasone versus pomalidomide and dexamethasone alone in relapsed/refractory. This was 117 patients, international trial. And at 9 months of median follow-up, found that the overall response rate, median progression-free survival, overall survival, VGPR, the median time to response, and the median duration of response all favored, again, the triplet. The grade 3 or greater toxicities were pretty comparable in those 2 groups. So talk to me a little bit about how this data might affect your practice. Kevin, we'll start with you.

Kevin: I'll just start with the pomalidomide, and I'll let Josh talk about the elotuzumab… Yeah, so I think the pomalidomide is, again, a wonderful option. So many of our patients are going to start out their therapy with lenalidomide and very often be on little, light maintenance. And a lot of our patients, as they relapse multiple times, are going to become resistant to lenalidomide. So it's nice to know now that we have another immunomodulatory agent because that really is one of the backbone drugs. But another agent we can use for patients who are a lenalidomide-resistant. And more so that we can use that in combination with virtually every drug that we've used in combination with lenalidomide, and use it in a triplet combination and get great efficacy in those patients.

Sandy: Great, and adding in a SLAM7 antibody, it looks to be fairly safe and effective. So talk about how you're using this in the relapsed/refractory population.

Josh: That's an interesting question because, where do we use it in the relapsed population? The use

of elotuzumab requires the use of an immunomodulatory drug for it to be effective. Now, we still have pomalidomide, it works effectively with that. The question kind of comes down to, it's when we're looking at newly diagnosed, first relapse. We're looking to get the deepest remission that we can for as long as we can. We have a great number of wonderful tools to reach for that can get it into a very significant response. When we look at elotuzumab, which is an effective drug and does work well with low impact on side effects, how does it compare—and it's impossible to compare studies—but how does it compare in outcomes to CPD or RVD or daratumumab combinations?

Josh: And so, when we're reaching for these medications, is there a significant lower level of side effects? Is there a significant lower level of infusion difficulties? Is it priced effectively? And does it have a significantly improved outcome? That's all the questions that we have to ask for every medication. And so when we look at elotuzumab, while effective, while very low profile on side effects, where can we put it in this where it can do the most good? And I think that's still a question that needs more studies to answer it.

Sandy: This gets back to our sequencing dilemma in the terms of the lack of really a standard algorithm as you mentioned in our prior session. And I think the other really important message for me listening to both of you is understanding how the study was done, how many prior lines of therapies did these patients have in these studies, and how do you then apply that data to your treatment decision-making in real life?

Sandy: So now let's move on to some of the novel agents that are not yet approved. A lot of very exciting data coming out of both ASH and ASCO. So, we'll talk first about isatuximab. So this is another anti-CD38 monoclonal antibody. And this was studied again, in a phase 3 randomized multicenter trial, looking at isa, as we'll call it, or isatuximab, combined with pomalidomide and dexamethasone. So again, one of those big backbones versus PD, or pomalidomide and dexamethasone, alone. And in this trial importantly, a large percentage, so 92% were refractory to 1 or the other prior agents in this trial at the median follow-up of 11.6 months. So a little bit earlier follow-up, obviously, getting ready for presentation at the meeting, which often happens. Meeting progression-free survival was superior by adding in the monoclonal antibody, as well as overall response rate, the depth of response in terms of VGPR, which we know is a criteria prior to transplant. And then beyond that achieving minimal residual disease negativity. The grade 3 or greater adverse events. So, again, always balancing safety, and efficacy was very comparable and tolerable in this isatuximab arm. So talk to me a little bit about how you began to incorporate now another drug that's in a similar category where today we have a single agent involved.

Josh: Well, I think it kind of comes down to... Kevin has brought up very correctly a number of times, doublets are not as good as triplets. And so when we have that situation, the question comes down to us, do quadruplets work better than triplets? And so when we look at this combination, we now have the opportunity to generate 2 regimens where we have a monoclonal antibody, an immunomodulator, a proteasome inhibitor plus steroid in the first 2 lines of therapy, with the potential of getting a significant reduction in disease. Again, it comes back to what we were saying earlier is, what's the order we use these things?

Josh: When we think about isatuximab, it has some of the similar problems that daratumumab does with timing infusion center and that's mitigated slightly by a reduced number of weekly doses, but an increased number of every-other-week doses. So well, the first 2 months are not as intensive; there is a period of time when daratumumab moves out to a monthly period and isatuximab stays on

an every-2-week period. So when we're having the conversation about treatment options with patients, we do need to make them aware of this model as it is going forward and the impact it will have on their quality of life, and their time spent in infusion. And also, at this time, we don't have a subcutaneous version of it. And again, and so we're looking at, well, not as long as the infusion time as daratumumab, still significant, but as an option of treatment whether it's in a triplet or a quadruplet; it's a very exciting addition.

Sandy: I think the other thing that will be really interesting to see is if there are any data to say that if you're refractory to one anti-CD38 antibody, you might respond to another. We know there are paradigms in other diseases where that is true, but I think that will be important going forward in looking at this data.

Sandy: I'm going to move on then to, I think, what I believe is one of the most complicated and challenging scenarios, which is where we have penta, what we call penta-exposed or triple-class refractory multiple myeloma. So we know that selinexor, which is basically a nuclear protein transport exporter, has been now studied, interestingly, in a mouse-model that was found to specifically correlate with multiple myeloma cell death. And so, this is drug, selinexor, it was studied in penta-refractory, where triple-class refractory, relapsed/refractory, multiple myeloma. So, these are people now that are refractory to an immunomodulatory agent, to a proteasome inhibitor or multiple proteasome inhibitors, and anti-CD38 antibody. They did not look at SLAMF7 monoclonal antibody in this study.

Sandy: And, we know that in this group of patients, survival is dismal. So, 3 to 5 months is the estimate. They can die very, very quickly in the absence of treatment. So, this STORM trial looked at these patients, and they found an overall response rate of 26%. They did a retrospective cohort review and found that 37% of these patients had received greater than or equal to 1 line of therapy, after their multiple myeloma became triple0class refractory. So, they have been treated once before they went on to the STORM trial with something. And then there were others that this was the first line of therapy after being considered triple-class refractory, and the median overall survival was better in the people that went directly to the selinexor arm compared to the people that have had other therapies.

Sandy: Now, they have done additional studies looking at the class or the way that this drug works. I know that it's been moved now, into the BOSTON trial, which is going to try to move it up into these people that have had only 1 or more lines of therapy, and that will be in combination with bortezomib and dexamethasone. So, we'll see where that takes us, but let's talk a little bit about adding a completely new class of drug into your repertoire, if you will, for treating this very difficult population of patients. So Kevin...

Kevin: I think, you hit it right on the head: a new class of drug. So, we have not had any new drugs approved for multiple myeloma since November 2015, and that was a new class of drugs. And so, having something novel is really important. So, we talk about this tetra-refractory group and we have a lot of those just simply because this is a disease that recurs over and over and over again. And so, we generally are doing something fairly novel to try and keep these patients going and/or getting them on clinical trials, which is a great idea, but very often it's, what can we do potentially to get these patients to maybe an allo transplant? It's about the only thing remaining for them. So to have something new, it's just absolutely exciting and hopefully on the horizon. I think about patients that look at that 24% overall response rate, that might not be so exciting, but I would again caution

to look at those and say, a great drug, which Josh was talking about, daratumumab. It's exactly what daratumumab had when it was first approved.

Kevin: And again, and that was in a group which was, at least triple refractory there as well. So, I think these are really exciting drugs, and I agree with you, the combinations are probably going to make it even better in a group that's less treated.

Sandy: And so, talk to me a little bit about your perspective of adding... Moving this forward now, in study, which is generally what we're seeing happen where it's studied in later lines of therapy and then begins to move up, how do you see that fitting into your choices for therapy, Josh?

Josh: Well, I really want to see what the results are of the BOSTON trial at this point because that's really going to define to us what it can do, where is this new mechanism of action, how is it going to really impact the status of disease, can we see in early, or early relapsed, can we see a significantly longer progression-free survival in this setting? But it does beg the question of what are we going to do with quad- and penta-refractory patients? I am always glad to see more effective treatments being moved upfront where we can get a longer progression-free survival, but where... I really would like to see what we can do. How do we get ourselves out of these positions that we're in? As you were mentioning, how do we piece something together until we can get a trial, how do we get something, how do we hold this patient in place until we can get them the best possible treatment? Is selinexor an option? It could be 24... 20% as you brought up, nearly as good as a daratumumab and that's about 30%.

Sandy: Great. So that leads us to the next abstract, which is looking at bridging people to something. And, in this case we're talking about CAR T therapy and relapsed/refractory multiple myeloma. So, one of the other very exciting abstracts was presented, and this is the bb2121, which is the CAR T therapy targeting B-cell maturation antigens and particularly shown to be effective against multiple myeloma cells in early studies. And so this is early-phase, multicenter trial, small number of patients, 33. But they had had greater than 3 lines of therapy. So talking about these therapies, these patients were heavily treated. In this case, they had received an immunomodulatory agent, a proteasome inhibitor specifically. The response was pretty phenomenal, 85%, however – and CR in 45% of those patients – however, there were 40% of the people in a CR who did eventually relapse. So wondering about that, being a final therapy certainly but the median duration of response was 10.9 months progression-free survival of 11.8 months and the presence of these CAR T cells was detectable beyond 1 year after that infusion.

Sandy: Now, we know CAR T is a complicated process, we know that there are adverse events that are related to the CAR T itself, including the cytopenias....the cytokine release syndrome and some of the unique neurological adverse events. So talk to me a little bit about your experience with CAR T, Kevin and Josh, and how you effectively manage those. We'll start with you, Josh.

Josh: Well, I think a lot of it comes down to AP education, because the advanced practitioner is going to be with the patient the most, and what we see with these CAR Ts in the same way that we saw with early bone marrow transplants is they need to be seen on a daily basis, monitored closely. We need to have education on the rather unique side effects that are coming out of not just this new medication but a lot of the new treatment options that they're not like the basic neutropenia, cytopenias that we saw; they are infinitely more complex, and I think the AP is going to play an enormously important role in this, in symptom management and information to the patient, because

a lot of this comes down to when we have the conversation with patients about CAR Ts, what's patient expectation in this setting? Through media, through popular media, they've seen that this is the silver bullet that is going to cure them, and while it is highly effective as you were bringing up, its durability at this point is in question. And so it really demands more study at this point. It is a good, potential treatment, but, again, it needs more research.

Sandy: So let's shift then to the last abstract here and talk a little bit in that light where we need more information about the other very exciting trial. A lot of people very excited about venetoclax and its use in multiple myeloma. And we know that the BELLINI trial looked very promising and favorable. Venetoclax is a BCL-2 inhibitor, so this would add a completely different mechanism of action. And we know, interestingly from laboratory studies that the BCL2 and MCL1 are additive sensitivity in multiple myeloma, so we can really have an enhanced benefit and particularly in patients harboring the translocation (11;14).

Sandy: So in this study, randomized, double-blind, they looked at bortezomib, dexamethasone plus venetoclax versus bortezomib and dexamethasone plus placebo. These were people with 1 to 3 lines of therapy. They then moved to the phase 3 BELLINI trial using that same platform. And in the interim results, there was a 2-fold higher risk of death in the patients receiving venetoclax and so the FDA halted that study. We do know that there was this subset of patients harboring the translocation (11;14) who had a much better response. Most of the deaths were related to sepsis, pneumonia, and cardiac arrest. And so this has been put on hold. We know that patients are always looking for things when there's something new coming. And I know in my practice, I've had patients who have the (11;14) who are on to myeloma blogs and other things asking, "Can I still get that drug?" So tell me a little bit about what you're doing in your practice to manage this situation where we don't have any new data yet.

Kevin: Right, I think it's important to point out this is not a drug that's approved yet for treating multiple myeloma, but I think there's a few takeaways from this particular study. And really to start off again, this is a drug with a completely novel mechanism of action for multiple myeloma. This drug has been used in other hematologic malignancies. So there is experience there. And the neutropenia, the infections are one of those things that are fairly common. So I think we can reach across the hall to our brothers who treat CLL and who treat AML. And the AML patients are probably more like our plasma cell disorder patients who have a higher risk of infection. So I think we could reach across there as well.

Kevin: I agree with you that probably the (11;14) is the group that is going to benefit most from this in terms of that. They have higher expression of BCL as opposed to the standard patient. And so I think it's when we think about using this drug, potentially off-label that we talk about all the risks and benefits and certainly, the group that I would say to use it in if you had that option would be the (11;14) translocation. But at this point, based upon these studies, probably not the other groups.

Sandy: And would you have anything to add to that, Josh in your practice?

Josh: The only thing – it's the perfect answer – but the only things I would add is at this point, I would be hesitant to use it outside of a trial.

Kevin: Absolutely.

Josh: And that the advanced practitioner needs to be very aware of the significant side effects and implementing protocols, prophylactic antibiotics to reduce those and close monitoring.

Sandy: Thank you both for joining us for this activity.

Sandy: We're now going to talk about some PEARLs or a recap of key points and strategies for practice application. We know that treatment options for patients with greater than 3 relapses is an unmet need. Some of the most recent clinical trials offer hope with agents with novel mechanisms of action, new combinations, new routes of administration, and newer cellular therapies. What can we do? We can apply understanding of the mechanism of action for each novel agent and novel aging combinations as studied in clinical trials to guide treatment decision making. It's important to restage the patient at each relapse because acquired mutations are common due to clonal evolution, and this will guide treatment selection and sequencing. We can integrate data gleaned from clinical trials and national guidelines to mitigate and manage treatment-emergent adverse events associated with novel agents, and to maximize duration of treatment, and as always, we can consider a clinical trial for any patient with relapsed/refractory multiple myeloma because we do not have all the answers and continue to have patients with limited or no treatment options.

Sandy: Thank you for joining us.