Sara Scott, PharmD (00:00)
Welcome to this discussion, everyone. Today we're going to be discussing implementing bispecific antibodies in multiple myeloma care. My name is Sara Scott and I'm a clinical pharmacy specialist with the Multiple Myeloma Group at Emory Winship Cancer Institute in Atlanta, Georgia.

Jaime Román (00:16)
And my name is Jaime Román and I'm excited to be a part of today's conversation. I am a community oncology physician assistant working at Texas Oncology in Plano, Texas. So as a community oncology physician assistant, I've seen firsthand how rapidly the treatment landscape is evolving in multiple myeloma, especially with the emergence of bispecific antibodies. These therapies offer real hope, but implementation, particularly in the community setting, has come with its challenges and opportunities as well.

Jaime Román (00:51)
So let me start with a quick patient story to frame our discussion.

We recently had a patient with relapsed refractory multiple myeloma who began treatment at a tertiary academic center with a bispecific antibody. After completing step-up dosing and achieving disease control, the patient expressed interest in receiving ongoing care closer to home. So that will be the background of today's discussion. This is where the discussion becomes real. How do we ensure the continuity of care without compromising safety or efficacy?

Jaime Román (01:23)
So my first question to you, Sara is, in your experience, what are some of the major barriers to implementing bispecific antibodies in general?

And then more specifically, what challenges exist with step-up dosing and transitioning to maintenance dosing.

Sara Scott, PharmD (01:40)
Yeah, I think this is probably the most important question to address first, so I'm glad that we're starting there. I kind of think of bispecifics in two different buckets, and this is maybe where my pharmacy mind comes in, but of course there's our clinical bucket. And there's a lot of challenges with these novel therapies. They came to the market hot and fast, and there's very limited knowledge for them if you don't use them every day, especially at those smaller centers or community sites that are dealing with things that are more than just myeloma and maybe have not used a cellular therapy before. So a lot of this might include what toxicities we should expect, but also when to expect them because the timing is different for all these products, and then how you prevent and manage those toxicities. I think in addition to that, identification of the appropriate patient for these therapies can be challenging if you're not familiar with that toxicity profile or comfortable with that toxicity profile.

And as of a few weeks ago, we now have three different BCMA bispecific antibodies on the market. So product selection and patient identification are going to add another risk. The biggest toxicities I think that are challenging and maybe scary for people that are not familiar with it are the cytokine release syndrome or CRS, and then the neurotoxicity or immune effector cell associated neurotoxicity syndrome or ICANS because that's just way too many words.

That's something that's really the biggest concern during step-up dosing. And that's where implementation at an academic center might be a little bit easier where they have experience with these things. Those centers might've been doing CAR T for a long time where we see these toxicities as well. So those tertiary or academic centers may be more comfortable with it. And these are really less of a concern for our community partners when we transfer back. So that's one big barrier that we've run into is that education piece of understanding what toxicities are gonna be pertinent when the community receives these patients back. So I think it's greater than 95 % of the CRS and ICANS events do occur during step-up dosing. And in my personal experience, I have not seen a case occur after the first cycle of therapy. And so it's very, very unusual that by the time these patients transition back, you're gonna see that. But there are additional toxicities to think about and manage, which are things we're used to, cytopenias, infections, but that doesn't make them not unique. That doesn't mean that we don't have certain strategies for how to implement this. So that's been a challenge as well. And I think that relationship between the tertiary center and the community center are extremely important in kind of passing along those protocols, passing along those recommendations. And we can talk more about that.

The second bucket, like I mentioned, is kind of that operational bucket. So all three of these, products do have a REMS program because of the risk for CRS and ICANS. So even though that risk is only during the initial step-up dosing, that REMS program applies to any healthcare setting that is gonna be dispensing this medication, as well as any provider who is gonna be prescribing it. So that operational detail can be challenging for community sites. Overall, these REMS programs aren't super complicated, but they still do take some legwork to get started up. So I guess to throw this question back to you is, Jaime, what barriers have you guys seen and what has kind of helped navigate those barriers when you are receiving these patients back from the tertiary centers.

Jaime Román (04:47)
Yeah, thanks for that awesome overview, Sara. I think first and foremost, I'm at a very large community practice within Texas. But the way that we have decided to roll this out across the state is by identifying some tertiary sites that are familiar with treating hematologic malignancies first and then letting them get their protocols in place and walking patients through it and the experiences and then ultimately slowly rolling it out across the state to the different community centers who are comfortable with administering the bispecific antibodies. What has slowed this down dramatically has been first and foremost reimbursement. So that's been very, very challenging from site to site. I think clinics and practices want to make sure that they're recovering any cost, especially when you have a drug that's very expensive that's sitting on the shelf. You want to make sure that you have everything in place and all your T's crossed and I's

dotted before you enter into this financial investment. So that's been a very interesting thing to navigate within our centers. I believe where it's really important here is to identify a practice champion within the sites who can really push these things along. And ideally that would be somebody with a clinical background. Doesn't have to be a physician, could certainly be an advanced practice provider or pharmacist, but somebody with a clinical background who understands the value of these therapeutics and can really push them along to the key stakeholders that are involved within the community setting. And that includes the hospital and the community clinics. There's gonna be key stakeholders within the pharmacy and therapeutics or the P &T committees where you're going to need to get them involved and have these discussions. And it may take several discussions and several emails and conversations to really win these people over and make them understand the value of having this sort of service at your community oncology setting.

I do know that biopharma has many different protocols and ways to help with the reimbursement aspect and to provide that sort of information to these sorts of committees. But this is where pharmacies are really, really critical and they can dive into the numbers behind everything. But really what's been successful is to have a clinical champion behind there to make sure that everything is moving in the direction to where they can finally offer these services and these therapeutics to patients.

Second, I think there needs to be a strong clinical protocol in place for ongoing management. So that often starts with collaborating closely with the tertiary center that initiated treatment. So ideally you want an open line of communication with someone at the tertiary center who has experience with managing bispecific antibodies.

So whether that's a hematologist, an advanced practice provider, even the infusion nurses, some context there where they can speak to each other. Thankfully, we have a wide network using online programs like Teams where we're all usually pretty available and speaking to each other. We obviously will call each other when it's necessary. But these types of questions or clinical vignettes as they come up are really, really critical to have people that you know and trust who are experienced and can kind of guide you through the ups and downs that may come up with managing patients long-term on the bispecific antibodies.

One quick plug for our organization is that nationwide we've developed a bispecific antibody playbook. So a bispecific antibody playbook that's been developed that has wonderful information on it that can be accessed online at any time by any provider. So if there's ever any question or issue, it's a great first reference, like a Bible to go to and read through when there are any questions.

And third, the community clinic needs to have a relationship with the hospital that can manage any sort of complications. Sara, that you mentioned that the majority of those complications are going to happen within the first and second cycle, CRS and ICANS being the major two therapeutic related risks that we see. So in this setting, when we are taking over for a patient who's really on maintenance and passed through those first few cycles of treatment, thankfully

that's not as common. But certainly something that we always need to be prepared for and make sure that there's adequate education and communication across all stakeholders. So whether that's managing hospitalists, whether that's oncologists in the clinic or inpatient setting, nurses, anybody that's going to lay their hand on the patient should really feel comfortable and educated and go through the necessary protocols to make sure that they're adequately able to treat this patient safely. Because that's first and foremost what we want to make sure happens is that we're accepting these patients and these patients know that they can trust that where they're ultimately going to receive their maintenance therapy is a safe and efficacious place to go.

And then finally, it's about building a cross-functional team. And so we're very fortunate at our center that we have wonderful open communication between our team of pharmacists and infusion nurses, advanced practice providers, physician leadership, are all aligned to make sure that the patient receives safe and seamless care. And so when that happens and when everybody is really on the same team and same platform, the little struggles or little things that can kind of come up seem a little bit easier to deal with because everybody knows that they're not running through these sorts of challenges on their own and they can lean on other people across their team to help manage these patients.

So, Sara, you mentioned the REMS program and many of these things, nursing, pharmacy, physician-led teams are very familiar with REMS programs, but are there any nuances or differences between bispecific antibodies and the products that are available or things that if you're just establishing, you're just getting started and you have all these products now, you said three approved BCMA targets now. Are there any nuances between them, things you need to know or how can we help us navigate and educate our team to make sure that that's a barrier that can be easily crossed?

Sara Scott, PharmD (11:17)
Yeah, I think, especially when you talk about myeloma, people think REMS and they think lenalidomide and they immediately retreat. So these programs are much simpler, but have some similarities. All three products have their own program. So, that interestingly has been an education point, even at our center that we have to enroll in each one. And that means both the site enrolling in each one. Every site will have a designated authorized representative that often is a pharmacist because it is very pharmacy heavy. So for us, it is our infusion center pharmacy management that is the authorized representative for the healthcare setting. But some institutions will have a physician or somebody else involved. The prescriber, however, cannot be an authorized representative. So that's something unique about these REMS programs and all three of them carry that feature.

As far as the requirements for the healthcare setting, they're all similar across the three different programs. So you do have to have an SOP in place for how you are going to make sure that you are compliant with the REMS program. And then there has to be staff training for everyone involved in the dispensing process. So that includes pharmacy technicians, your pharmacists,

as well as we at our institution will include our infusion center teams. And they are required to all attend the same training sessions so that everyone understands the REMS requirements.

The other thing that they all have in common is they all require an RDA, REMS dispense authorization code. And that is for every single dispense of the product, whether it's a step up dosing or a maintenance dose. One nuance that is new with the newest product, linvoseltamab, is they now allow for a single RDA for the same physician-patient partnership.

So for example, if one patient sees the same provider every time, that provider is who signs their orders every single time, one RDA can be obtained with the first dispense and used for every dispense. But as soon as a new provider signs that order, they do need a new RDA. So for our center where we have eight physicians and eight APPs, that gets a little hairy, but for some smaller centers that may decrease that workload of that REMS program.

And then the other half of the REMS program is the provider enrollment. This fortunately is a one-time enrollment, but this is where our confusion has come in is our providers are like, oh my gosh, this is the same quiz for another program. Why do I have to do this? And it is the same knowledge assessment, but it is separate for each program. So there is a training module that all providers should complete. It's essentially reading through a PowerPoint that explains what the product is, what the risks are, the incidence of those risks, the timing of those risks, and then completing a knowledge assessment.

And then the other piece of the provider requirements is the recommendation that all patients receive education on the risks of these therapies, as well as a wallet card. I describe this to patients like an allergy bracelet. It lets everybody know you're on this medicine because if you present with a fever, it may mean a lot of things in a patient receiving a bispecific antibody. So that doesn't have to be done by the provider. That's allowed by a delegate. And that's all three programs, again, the same thing.

They all provide a nice wallet card. There's printable versions. If you call your MSL, you can get the lovely not printable versions that actually fit in the wallet. So those are readily available. But I think the big heavy lift is at the start of these. But as you get through the programs, at least for the provider side, not a lot to do. There are audits for all three. The audits are all very similar as well. So they're checking SOPs, training logs, drug management logs and making sure those drugs are being handled appropriately. And then in our audits, they've also kind of followed a patient and made sure RDAs were obtained appropriately, similar to like a JCO audit. So those are things to be prepared for as well. And as far as resources for prepping that, I mean, you can lean on your tertiary medical center that you're receiving these patients from to ask for those SOPs. I sent two emails today with our SOP to two different community sites that we've partnered with. Then also leaning on again, the manufacturers and those MSLs, they are there to help you get set up with all of this.

Jaime Román (15:20)

Awesome. Yeah, so we're going to take a little bit of a left and talk about something a little bit more exciting than REMS programs and hit on adverse events. So particularly later toxicities. I mean, I know that this is something that, you know, when you hear bispecific antibodies, especially something that's just unfamiliar in the community, you hear about ICANS and you hear about CRS and you worry about, you know, what kind of things are we going to see when it's something brand new in the community? So, what should clinicians be aware of and what should we be prepared to manage when we accept these patients?

Sara Scott, PharmD (15:57)
Yeah, I think this is part of those protocols that need to be developed too, right? And considering these toxicities. So again, kind of big bucket toxicities that are across the class of these therapies are cytopenias and infections. And then there's a couple of nuances that I'll talk about as well. But for cytopenias, these do seem to be early toxicities. And there's a lot of theories as to why this is. Is it driven by the inflammation? Is it just because we're obtaining disease control and kind of clearing out the marrow to make space for producing new healthy cells? No one fully understands why, but it doesn't seem to be a forever side effect. So because of that, really utilizing your supportive care, such as filgrastim for neutropenia, which is gonna be your most common cytopenia, or considering support of your platelets as well. We use a lot of romiplastin at our institution.

And these are temporary measures that can allow you to continue therapy and kind of power through these cytopenias. And I think that's a huge education point that we've provided to a lot of our community partners is we don't need to hold therapy for those cytopenias all the time. There are cases, of course, but for the most part, if we think it's disease driven, we should try and support them through it and do that with supportive care like filgrastim or romiplastin or things like that.

Anemia is less common, something we do see, especially if it's disease-driven, but I would say neutropenia number one for sure, and then thrombocytopenia as well. Considering the neutropenia, if you do have a patient who's neutropenic, of course, prophylaxis, especially febrile neutropenia prophylaxis with something like levofloxacin definitely should be initiated. And then we will consider fungal prophylaxis with something like fluconazole in patients who have prolonged neutropenia.

Maybe we have a delay in getting them that growth factor. The growth factor isn't quite working, because we have it at the wrong cadence or something. And so those are all considerations as well. Again, with time, this does seem to improve. And so we often can take patients off these therapies. And that's reassuring to patients. They don't want to keep adding on all these treatments. So it's something that's a temporary measure to continue on with treatment.

And then the second piece is infections. So this is huge. In the clinical trials, the numbers were really high and grade three to four infections occurred in 40 to 70 % of patients depending on which product and which registrational trial you're looking at. So what has come from all these

findings, especially those earlier trials, is that Zoster and PJP prophylaxis are recommended for all patients on a bispecific antibody.

And then the newest hottest data, is the implementation of primary prophylaxis with IVIG. So not waiting until their immune globulins drop to less than 400 and true hypo-gam, but really initiating that early. And at least at our institution, we've shown that that has significantly reduced the incidence of infections, particularly those severe hospitalizations requiring grade three to four infections. So that's become really important.

And then another hot topic is the discussion of CMV. And Jaime, I don't know how much you've talked about this, but it's becoming a very big topic. We are seeing high rates of CMV reactivation, but reassuringly that CMV reactivation doesn't seem to require treatment. So we have not seen a single case of CMV disease. We have started a few patients on preemptive therapy for a variety of reasons, but nobody is developing CMV disease. So we're monitoring for it.

I think it's still a big question, a research question of exactly what to do with it, but that's become another topic. As far as medication, kind of specific things to think about, because there are some nuances among the three. CRS rates do vary among the three. Again, that's one of the earlier side effects, but they do vary. Infection rates are very similar across the three.

For some reason that is not fully understood either, elranatamab seems to be associated with some other neurotoxicities, such as neuropathies, especially in patients with pre-existing neuropathy. So that's something that we've kind of taken into consideration when thinking about product selection. We're not, again, not sure why that is, but we have not seen that quite as much with the other therapies. I've also seen skin rash with some of these, and it does seem to be immune mediated. So I often compare it to some providers as, kind of those PD-1 rashes that you see that are immune mediated, give them some topical steroids, they seem to calm down and seem to be early on in treatment. So the big things again, cytopenia is infection, but a couple of other nuances that we see as well.

Jaime Román (20:31)
Yeah, I just want to add where you're going here to just some awesome points. As far as the IVIG, I totally hear you there because I think we're so used to it in the community, especially when were following and managing patients with CLL with hypogammaglobulinemia. You're watching for the sign of pulmonary infections. You're watching that total IgG level go down. But you don't really think that a patient with multiple myeloma may need IVIG, especially when their IgG levels are normal. But you have to remember that those IgG levels are non-functional, so it doesn't really matter what that level is. What we've gotten accustomed to is checking for the subclasses, especially if you need to try to push approvals for IVIG in this patient population is to check IgG subclasses.

And then, yeah, the CMV reactivation, it's comforting to hear you say that it's not requiring treatment because it's pretty scary when you're already dealing with patients with high risk infections. So, yeah, just wanted to add those types of things that we're seeing clinically.

Sara Scott, PharmD (21:38)
Yeah, I'm glad you mentioned the reimbursement because when you mentioned reimbursement with the drug itself, I thought of IVIG and we have a lot of insurance battles where they see the IgG level is 5,000, but this patient has an IgG myeloma. So that's like you exactly, you said it's not functional, it's not doing anything for them, if anything, they're higher risk. That's definitely been a barrier to us getting IVIG for some patients, but I think with updated guidelines and updated data that's coming out constantly, I think insurance is more open to it. Awesome.

So last kind of question to wrap up is what are kind of some big takeaways that providers should have for day-to-day management of this and what things do you think that providers really need to know as they're kicking off this therapy and managing their patients?

Jaime Román (22:25)
Yeah, so the first community provider that's out there listening to this podcast, I want to reassure you and give you hope and quell any sort of fear that may be inside you and let you know that this is very, very feasible to handle in the community setting. Way back when, rituximab was coming onto market, I know that there was a lot of fear about monoclonal antibodies and how that was going to be administered and handled within the community setting. And now those medications are just, they're like seasonings. We just sprinkle anti-CD20 on any sort of heme malignancy, lymphoid malignancy, and it's become second nature. Certainly once you get past the step-up dosing and through the woods, so to say, for the neurologic toxicities and the CRS. Very, very feasible and manageable to handle these patients. These patients do quite well, and it is well tolerated. You do have to watch out for infections, and so we cannot hammer that point enough in that these patients are at baseline high risk for infection, and when you're manipulating the immune system like we are, it's just certainly a high, high risk situation. So, that's where patient education is key. I think sitting down and really walking through the ins and outs of what this therapy is, what we're trying to accomplish with the immune system, and what the big risks are that we see later on. Because if the patient understands what the situation is, they're more apt to make sure that they're being extra cautious in higher risk situations to avoid infections. So that's really big. And then regular monitoring is key, especially for those cytopenias and infections. Now, I think we really established this in this conversation that late onset toxicities can happen. And so we always have our antennas up for those types of things. And where it becomes really, really critical is the handoff in the community. you often may have a physician or an APP team, or the team I'm on has several APPs that support one physician. So you want to make sure that your documentation is clear and that you're communicating constantly within your team members so that really everybody's on the same page and understands how patients are doing week to week.

Coordination with pharmacy is also critical and drug administration schedules. I mean, as we kind of get into the later stages of maintenance, the administration calendar can kind of change.

And so making sure that we're working with pharmacy and their team very, very closely to make sure that we're all on the same page is that, and it's been clearly communicated in the EMR. And then lastly, you know, resources from pharmaceutical companies can be very, very helpful. no offense to those pharmaceutical companies that may be listening, but oftentimes when you hand me something, I'm going to immediately throw it into the trash can. But when it comes to these types of things and scheduling and dosing and toxicity, there's some really beautiful and really informative handouts that the companies have put together. So I have a whole stack of them in my desk on bispecific antibodies that I just will refer to from time to time and sometimes even bring it into patient conversations so that I can kind of illustrate what I'm thinking about and what I'm working through when I'm working with these patients. And so that's what I really say is just clear communication with your team and with everybody involved and making sure that the patient understands and is well educated as they continue on this therapy because what we're saying is these aren't going to go away anytime soon. These bispecific antibodies are here to stay. They're incredibly powerful and effective, especially when given the right setting. And so making sure that everybody's well-educated and ready to go will be critical as well.

Well, that brings us to a close for today's conversation. Thank you so much, Sara, for a wonderful overview and conversation in implementing bispecific antibodies in the setting of relapse, refractory, multiple myeloma. And thank you for joining us in this important conversation. Bispecific antibodies are transforming how we treat relapse and refractory multiple myeloma. With the right partnerships, planning, and education, we truly believe that community oncology clinics can play a major role in expanding access to these life extending therapies. It's an exciting time and we look forward to seeing how these efforts evolve in the months and years ahead.