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The Weight of Recurrence: Navigating Multidisciplinary Care Planning in Recurring/Metastatic Cervical Cancer

Announcer:
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Dr. Slomovitz:
This is CME on ReachMD, and I'm Dr. Brian Slomovitz. Today, Dr. Robert Coleman and I are discussing metastatic cervical cancer. We'll be looking at clinical trial evidence for immune checkpoint inhibitors and antibody-drug conjugates, treatment selection and sequencing, and multidisciplinary care for managing adverse effects.

Welcome, Dr. Coleman.

Dr. Coleman:
Thanks, Brian. It's great to be here with you, and thanks for moderating this program.

Dr. Slomovitz:
Yeah, no, thanks for being here. I'm really excited for this conversation.

In recent years, the treatment landscape for recurrent or metastatic cervix cancer has really undergone significant shifts. Most notably were the approvals of first-line pembrolizumab plus the platinum doublet, with or without bevacizumab, as well as a second-line treatment of use of tisotumab vedotin. These FDA approvals have set a new standard in the management of recurrent or metastatic cervical cancer. It really challenges clinicians to choose the optimal regimen for their patients.

Dr. Coleman, let's first discuss the treatment selection and sequencing with the checkpoint inhibitors and the ADCs for relapsed cervix cancer. Please, first describe for us biomarker testing and logistics of biomarker testing. And how do you incorporate that into your treatment selection?

Dr. Coleman:
Yeah, thanks, Brian. This is a great topic because it's continually evolving as more options become available for patients with recurrent disease. But I'd say up front, along with histology, we're getting some various other parameters such as PD-L1 staining that helps annotate the tumors itself. I think we know that most of these, particularly the patients that we see in GYN squamous cancers and adenocarcinomas, have high expression of PD-L1.

But with the addition of, as you mentioned, the ADCs, expression of other epitopes on tumor cancer cells that might be relevant for the use of upcoming antibody-drug conjugates is becoming more of interest and certainly something we would want to pursue. Not all of them are linked to it, but at least some of them now optimally provide options for people wanting to participate in clinical trials.

Dr. Slomovitz:

Right. So you're talking about PD-L1 testing, so obviously, there was a KEYNOTE-158 study that brought pembrolizumab into the recurrent setting. That was based on PD-L1 positivity and that really changed the second-line care until we incorporated it into the first-line care with [KEYNOTE]-826. PD-L1 positivity, really changing the world there, incorporating pembrolizumab in the first-line management and seeing the benefit there.

Talk to us a little bit about that and, really, how has pembro, first of all, changed the world of management of these cases?

Dr. Coleman:
Well, I think it ushered in an incredible migration of potential benefits to patients kind of going forward. So, as you mentioned, immune checkpoint inhibitor therapy was evaluated across several different immune checkpoints. Pembrolizumab obviously coming into the scene very quickly because of its pan tumor indication. And so, yes, we saw objective response rates, but probably even more important in what we're probably counting on for an immune system is a better ability of immunosurveillance.

And so while the response rates weren't all that impressive, they were associated with these extraordinarily long and unexpected duration of responses. And so that provided us a lot of confidence to start looking at the combinations, as you mentioned, that moved into the KEYNOTE-826 regimen, which was adding to essentially our best standard of care, which was paclitaxel-carboplatin, usually in combination with bevacizumab.

So that trial, which, I think, was really a well-done trial, to be honest with you. It's one of my favorite trials to use for teaching because it evaluated in an analytical way every single endpoint that we would be interested in, including the overall objective response, the duration of that response, progression-free survival, and then the home run, overall survival.

So that was really a telling connection between a tumor that has a predilection for response to this kind of therapy and then ultimately what the response was.

Dr. Slomovitz:
Thanks for that, Rob, and really highlighting the importance of adding pembrolizumab in the second-line and the first-line, and we even saw with [KEYNOTE]-A18, incorporating pembrolizumab into the management of patients with locally advanced cancers with the overall survival there.

While that's all going on with pembro, though, you really did a lot of work with tisotumab vedotin and the tissue factor ADC. Can you talk a little bit about how that came into – really, we talked about FDA approval and we talked about biomarkers. Does that biomarker matter, the tissue factor biomarker?

Dr. Coleman:
Right. So it's a really good point. I did mention a little bit about this in the intro, that not all these ADCs necessarily are required to have expression of the factor as a biomarker for inclusion. Tissue factor is so ubiquitously expressed that it was felt that it wasn't necessary to actually test for it because we just expect it, almost like we expect PD-L1 to be positive in cervix cancer tissues.

But, yeah. This was a great story. I love this story because it started back – literally an idea on a napkin at an ASCO meeting several years ago and then emerged into this development of a clinical trial program that led to accelerated approval followed by, recently now, the report on the [innovaTV]-301 trial, which was the randomized trial versus investigator's choice chemotherapy. Again, another really great story with respect to how it impacted our patients and really added to this, like, total overall experience in primary and recurrent disease for cervix cancer patients where we've seen, essentially, a tripling over historical overall survival expectations for our patients.

Dr. Slomovitz:
Yeah, no, really exciting work. And we talked about the FDA approval. I personally think as pembro moves earlier and earlier into the locally advanced setting, we may see opportunities for tisotumab vedotin to even go earlier than the second line. I know there are some combination trials going on. I'm really excited about combining TV with either pembro or carbo. What are your summary thoughts on that?

Dr. Coleman:
Yeah, I think so too. If we think about this as an effective way to give a chemotherapy agent, these combinations would be really relevant to explore further, and of course, we have seen from some preliminary data in the phase 2 setting that there are some acceleration of our expectations for responses for both these combinations.

So, yes. I'm encouraged that we can continue the story and continue to move the most effective agents to earlier and earlier lines of therapy.

Dr. Slomovitz:

It's real exciting, and we really touched a lot about the efficacy. Let's shift a little bit. Let's talk about monitoring and the management of the adverse effects in metastatic cervical cancer treatments, particularly the management of immune-related adverse events, which necessitated a coordinated, really, multidisciplinary approach. A lot of times, we work with our healthcare team members in helping to manage this. I know I work closely with not only my nurse practitioners and my pharmacists, but the eye doctors as well that work with us.

Tell us a little bit about how, some of these immune adverse events that you've seen, how you're managing them. And really what I want to focus on: we saw the data, but once we get used to the data, the management and the studies, in the trenches, my mitigation strategies work because I'm ready for them, I'm prepared for them, and they seem to limit the toxicity.

What are some of your thoughts of what you saw in the trials and how they're playing out now in practice?

Dr. Coleman:
Yeah. It's a really good point. One of the things that we see when we expand from a clinical trial setting where not only is patient selection so tightly controlled, but the evaluation, discernment, and management intervention of adverse events that occur on trial are different than what happens in the real world, so it's kind of interesting that you say how does this look like in the real world or in the trenches, as you say.

I think a lot of us in the GYN/oncology sphere started to get more and more experienced with these immune checkpoint inhibitors largely because of our experience in cervix cancer and endometrial cancers we mentioned before. And we leaned a lot on our colleagues who had a lot of experience with this in non-GYN tumor types such as lung cancer and melanoma and learned a lot about that. And so I know when I started to be using these agents, we adopted kind of a programmatic approach to this involving our colleagues to help us with potential immune effects.

And obviously, the ones we were most concerned about were things like colitis and interstitial lung disease, rash, and neuropathy. And those were not common things that we were necessarily accustomed to, but we were concerned because of the potential with interactions with radiation; it's something that we already deal with in cervix cancer patients.

So, yeah. How I deal with it is it's gotten to be much more of an experiential advancement, so better classification and patient education. And then there are a number of guidelines now that are in print that can be resourced online as well that can help clinicians actually work through the toxicity management for the ones that we see typically.

Dr. Slomovitz:
Yeah. No, I think particularly with immune-related ones, we're getting more and more used to them and navigating through some of the side effects what we see.

I introduced it; I'll talk about it briefly: the ocular side effects that we may see with some of the ADCs. And I think to the points we're discussing, the multidisciplinary care, getting educated early, getting the team coordinated early, getting the patients to see an eye doctor sooner than later, and aggressive ocular mitigation strategy with the steroid drops. Simple things like no contact lenses, lubricating the eyes. In the studies, we saw that the time to onset of this side effect was just over 1 month, but of those that had some issues, 85% of the affected patients had complete or partial resolution, so.

Dr. Coleman:
And that's important.

Dr. Slomovitz:
Yeah. If we knew about it and we followed it, it could resolve.

Dr. Coleman:
Yeah. I mean, you probably hear this side; I mean, I heard from my patients. We'll talk about this drug, and they say, "Oh, I heard that causes blindness." We know that there's a lot of education. This comes actually from not only just the patients, but some of the people who really have a lot of experience with these agents.

So how do you respond to that? When a patient comes and says, "You know what? I heard this will make me blind." Or let's say, "Listen, I already have trouble with my vision. I'm really afraid about taking this medication. Like I have cataracts, or I have poor visual acuity."

Dr. Slomovitz:
Yeah, no, that's an important point. And we get this question, like, every day that we prescribe this. We talk about the risk-benefit. We talk about the fact that it's an effective drug in cervix cancer, and there aren't that many effective drugs. And we talk about the fact that we're going to watch it closely. I mean, not to use a play on words, but we're going to keep an eye on it, right? We're going to really

watch out for any of the side effects. We're going to incorporate the care of their ophthalmologist. It's important as a treating oncologist to get on the phone with their eye doctor, whether it be an optometrist or ophthalmologist, because they don't know what it's like to treat patients who are on this drug because it's so new.

So it's really the team approach that we keep hammering home explaining to them they're on an ADC that has some ocular side effects. This is what we recommend. This is what we're following. And by doing that, I feel that we could help the patients increase the exposure to the drug, limit the side effects, and strike away that fear of blindness or other things that really probably won't happen to begin with.

Dr. Coleman:
Yeah. That's super important, right? Because we know that these are events that can happen. We know we need to balance out what the fear is, but it's really important that we keep patients on treatment that we think's working for them. And that's where we see the potential benefit for long duration of response.

Dr. Slomovitz:
We talked a lot about the current therapies; we talked about how to manage the side effects of the current therapies, how important that is. Briefly, towards the end of our time here, let's talk about what's in the future. What are we going to do now that we have these FDA-approved drugs? We are still doing a lot of research. Tell us a little about what trials are maybe ongoing that you're excited about, directions that you're excited about, and what our next steps may be.

Dr. Coleman:
Yeah. I think you already kind of mentioned the two kinds of major classes are what we can do to augment immunotherapy. Is there an opportunity for – in a post-IO world, and it's, obviously, there are some new compounds that are coming down that are co-targeting things like CTLA-4 along with PD-1 or VEGF and along with PD-L1, and these are really exciting because these are opportunities that we have to potentially mitigate both toxicity and increase efficacy.

So that's kind of a cool opportunity to have this and other immune checkpoints that have been evaluated. Some of these are in active clinical trials, such as TIGIT and LAG-3. We'll have to just see how those fared out. We haven't seen the same kind of broad crossed solid tumor efficacy with some of these additional immune checkpoints that we've seen in cervical cancer so far. I know there's some promising signals with some of these to go forward. I think that the expansion of the ADC space and, as we already spoke about, additional combinations with tisotumab vedotin, obviously, represents some really cool and interesting opportunities going forward.

I think the one thing that's been, in my sense, that I am excited about is the return to the potential for vaccination. So you remember when we started about prevention, obviously, the cervical cancer vaccine has the potential to eliminate this cancer altogether, which is really our goal. But developing therapy and vaccines have been extremely difficult, and so now we've started to see some of the emergence of some novel technologies that potentially may take advantage of a potential vaccination strategy as well as the use of cellular-based therapies, which obviously would kind of be the other end of spectrum for complexity to potentially impact long-term outcomes and what I always like to term is immune surveillance. Those are the types of things I think would be super exciting kind of coming forward.

Dr. Slomovitz:
Yeah, and that's so exciting. I always love doing these with you, Rob. I always learn so much about what's going on, what the latest and greatest is.

We each have time for one take-home message before we finish up. I'll take the prerogative and go first.

It's such an exciting time, right, with the approval of TV, with moving IO earlier and earlier in lines of therapy, the old days of telling our patients with cervical cancer that their time is really limited. It is a deadly disease, but we're making small baby steps, and along the way, it's going to turn into giant steps. So I'm excited to be giving our patients the opportunity to get these drugs.

Dr. Coleman:
Yeah, I always go back to kind of the mantra that I think I stole from you years ago, decades ago, is that research cures cancer. So if you have the opportunity to participate in clinical trials, please, please, please consider it. From the days of single-agent chemotherapy back in the late '80s, early '90s to the recent BCC report and KEYNOTE-826, like I said before, we've tripled the expected overall survival for this patient population. Same patient population, but in this period of time, with our experience and our commitment to clinical trials, we've actually significantly impacted this population, which was in desperate need of effective therapies. So that's my take-home message.

Dr. Slomovitz:
So close. So much to do, so. But that's all the time we have today. So I want to thank our audience for listening in, and thank you, Rob,

for joining me and sharing all of your valuable insights. It's really been great speaking with you today.

Dr. Coleman:
It's been great, Brian. Thanks so much, and I really appreciate the invitation to join you.

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