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5 Things You Need to Know in Cervical Cancer: New and Emerging Agents

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Welcome to CME on ReachMD. This activity, entitled “5 Things You Need to Know in Cervical Cancer: New and Emerging Agents” is provided by Prova Education.

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Dr. Coleman:
This is CME on ReachMD, and I'm Dr. Robert Coleman. Today, Dr. Kathleen Moore and I will be discussing the increasing complexity associated with managing patients diagnosed with cervical cancer who have failed first-line therapy.

Welcome, Dr. Moore.

Dr. Moore:
Thank you, Dr. Coleman. It's my pleasure to be here.

Dr. Coleman:
Dr. Moore, first and foremost, what is the global burden of cervical cancer, especially for our patients who have failed first-line therapy?

Dr. Moore:
The global burden of cervical cancer is immense. There's a half million cases diagnosed every year, the burden of which are in the developing countries due to all the reasons that we know: lack of access to screening, lack of vaccines, et cetera. And a quarter million deaths. And so the burden is huge and basically one of the highest unmet needs in medicine, in my opinion.

When you think about women who present with cervical cancer in this day and age, especially in developing worlds and still in the United States, you know, who presents with cervical cancer? It is largely a very, unfortunately, homogeneous population of women, for whatever reason, just have not had access to care, have been historically excluded from access to care, or marginalized in some way that's prevented them from accessing screening and also have not received the vaccine. So in the United States, it's a very rare disease, only about 12,000 new cases a year, the majority of which are low stage. You do have these incident cases that escape screening, but you pick them up on routine screening and HPV testing, and those are curable. And then you have about 3,000 to 4,000 that present still with these local regionally advanced cancers not dissimilar to the developing world, where they need high-quality chemotherapy and radiation in order to cure. And that's not available everywhere here, and it's certainly not available everywhere in the world. When we fail to cure, patients don't fail. We fail them. So when we fail to cure, the burden here is immense for a number of reasons.

Dr. Coleman:
Yeah, I'm glad you brought that up. I think that as we think about the WHO’s initiative on eliminating cervical cancer, you have to look at this from 2 ways. As you mentioned, there's the vaccination component for the prevention of, and then there's improving the standards of care for existing patients who have the disease. Obviously, we've got this issue with getting the best therapies and distributing it

equitably around the world.

Dr. Moore:
Now that we have a clear picture of the burden faced by our patients with cervical cancer, especially those whose tumor has failed frontline therapy, what do we do for a patient who had stage 3C1 cervical cancer, she's just gotten chemo/rads, maybe not brachytherapy, so sort of this quasi-treatment, and it's not gone?

Dr. Coleman:
We consider all of the factors that surround that patient. So their health, their desires for treatment, the location of their recurrence or the progression, the type of therapy they received ahead of time. All those are factors – their performance status – those are all factors that we consider when we make that treatment decision. And ultimately, we do settle on the modalities that they haven't received. So if they've had surgery without radiation and recur, then that's something we would go to, chemoradiation. For those patients who have had optimal therapy in the frontline setting, then we started thinking about combination chemotherapy. And of course, we've had a tremendous explosion, if you will, of interest now in looking at ways to modify our existing standards of platinum-based combination therapy, now adding bevacizumab and then most recently adding pembrolizumab.

And I think it's quite telling if you go back to the ‘80s through the early ‘90s, mid ‘90s, we saw almost no change in overall survival despite all the randomized trials we did. Then we added bevacizumab, and we saw about a doubling, almost a doubling of the median overall survival. And then we added pembro, and we saw a tripling over that time period. Much of it being in the last 15 years.

For those patients who, let's say, had already gone through chemotherapy, it kind of leads us to the next layer of therapies. And obviously, we've been very excited about the antibody-drug conjugates, specifically tisotumab vedotin. And now this has been approved and is out, and physicians are using it and getting more experience with it. And so we've seen some really objective and durable responses for this treatment. And we're excited about that as adding to our armamentarium, and we continue that development.

Dr. Moore:
So let me just sort of pressure test this. You mentioned that we have improved overall survival, which is exciting. And it's true with bevacizumab and now with the addition of pembrolizumab based on the KEYNOTE trial, 826. So why can't we move that up to prevent these treatment failures? What's the thought about using immune checkpoint inhibitors with chemoradiation? Wouldn’t that cure more patients?

Dr. Coleman:
Yeah, it's a great idea. And we have a lot of ongoing trials, one of which we'll hear about very soon, the CALLA trial. But we also have – KEYNOTE-A18 is another trial that's looking at 2 different immune checkpoint inhibitors that are being added to the primary therapy for high-risk patients.

I don't think we know the story completely about what radiation does to antigen-presenting cells and whether or not that's the most effective strategy, combination or sequential, maintenance versus maybe combinations. All those are unknown questions. But I do know that the CALLA trial reported out in press release that it did not meet its primary endpoint. So we'll have to dig into that trial a bit more once the data are known and published.

Dr. Moore:
Yeah, absolutely. It was a surprise. So we'll see what A18 shows us.

Dr. Coleman:
For those of you just tuning in, you’re listening to CME on ReachMD. I’m Dr. Robert Coleman, and here with me today is Dr. Kathleen Moore. Our focus is on achieving a better clinical understanding of the increasing complexity associated with managing patients who fail first-line treatment for cervical cancer.

So building on our last question, what is most important for our learners to know about emerging approaches for the management of second-line and later cervical cancer?

Dr. Moore:
So when we talk about second line, we're typically talking about tumors that have received sort of frontline metastatic treatment with combination chemotherapy and bevacizumab or immune checkpoint inhibitors. So tumors have progressed following that. And now we call this second-line metastatic or third-line metastatic. And really, I mean, I'm old enough to remember a time where basically the answer was nothing. I mean, we had a laundry list of monotherapy cytotoxics with really marginally, if even that, expectations of efficacy. And now we actually have options for patients.

So I think when you encounter these, which we all do, you have to think about it from a few angles. Number 1 is that these recurrences

are complex. A lot of times these women have received whole pelvic radiation with brachytherapy or maybe incomplete radiation. Unfortunately, we see that in my part of the world quite a bit. And so the recurrences are in this radiated or quasi-radiated field and very problematic from a symptom management standpoint with ureteral obstructions and fistulas and quality of life issues that are really unimaginable. And these happen in the developing world, as well, where they have even far fewer access to any kind of mitigation strategy to help unblock someone's ureters or you have a draining fistula, so that they could consider therapy.

So for this group of patients, I do really think that you have to balance expectations of efficacy with expectations of improving quality. And fortunately, in the United States, we do have a lot of things we can do to try and mitigate these.

And then what is she eligible for? We have, if she's not seen an immune checkpoint inhibitor, say was pre the approval, then we have approvals for pembrolizumab in this setting with a response rate that's pretty low. It's only about 17%, but a duration that's quite long and disease stabilization that's quite clinically meaningful.

Dr. Coleman:
Is that biomarker restricted?

Dr. Moore:
Yes, it's biomarker restricted to just those that are PD-L1 positive. Thank you for mentioning that. Really, those are all the indications for immune checkpoint inhibitors. So we have to do that testing.

In the patients who are post-immune checkpoint inhibitor, so presumably immune checkpoint inhibitor resistant, we have a new class of drugs, these antibody-drug conjugates, and tisotumab vedotin is now FDA-approved via accelerated approval; the confirmatory trial is ongoing. And this is an antibody-drug conjugate that targets tissue factor and has a cytotoxic payload on its tail. And we do not have to tissue test or biomarker test for this particular drug. And the efficacy is really better than any other single agent we've ever tested. It's about 24%, with a median duration that's above 7 months. And but again, if you look at the approval and you look at the waterfall plot, you had about 24% cross that 30% mark. But you had a large percentage of patients who had decrement in their tumor dimension, and that likely would contribute to improved quality of life. And so I think there's more to the benefit than just response rate. And I think that's important for patients to hear, as well, because they say 24% response rate, that doesn't sound really good.

Dr. Coleman:
I like to highlight that because when we treat patients – we treat patients, hopefully we'll get a response. But when we treat patients prospectively, what we're doing is treating them until we know that it's not working anymore, which is progression, right? So that, what you just mentioned, 70% of the patients on that phase 2 trial did not have a progression at their first full assessment. So that does speak to the fact that this particular agent is actually adding to our treatment paradigm.

And of course, this field is expanding in many different lines of immunotherapy. We're going to hear about the combination of ipilimumab and nivolumab, which seems to have some interesting activity. We have evidence of a new HPV-targeted vaccine that's going to be given with pembrolizumab that looks like it has some interesting activity. We have TIL-based therapy, right?

Dr. Moore:
TIL-based therapy, I think, is very, very promising. The data in the recurrent setting was a 45% response rate and still even more patients with these spider plots that went way out. And now that's moved into a frontline cohort. And very excitingly, that particular trial has just opened a cohort for post-immune checkpoint inhibitor progression. And so we'll see if you can salvage post pembro, you know, get an overall survival benefit. And then if TILs can kick in there and really prolong that, that would be kind of magic. But we have to acknowledge that even in, kind of, resource-rich US, it's not an easy thing to do. You've got to harvest enough tumor, I mean like a centimeter cubed of tumor, you can't hurt someone with the surgery, and then there's this lead-in to make the TILs. And that, at least currently, is not a widely available therapy.

Dr. Coleman:
Great. Thank you.

Dr. Moore:
So what do you anticipate being the next change in the standard of care here?

Dr. Coleman:
So we kind of follow this playbook that we have adopted for many years. And you mentioned, when you were talking about single-agent chemotherapy, you remember back in the day when we were screening drugs, one after another, in these phase 2 trials, looking for something that had better activity than our existing standards, and some – with a pretty low bar. But, you know, paclitaxel got there. Platinum obviously got there. Bevacizumab got there. And so we iteratively moved those into earlier lines of therapy – KEYNOTE-826 is

a good example of demonstrating that we had another drug, pembrolizumab, which had a 14% or so, a 15% response rate as a single agent. Bevacizumab had about the same. We added those, and we ended up with this 4-drug regimen that showed that it was better than existing standard of care. So that's our process.

So the idea is to continue to discover, hopefully to bring the biomarkers, the ADCs if they're annotated. You mentioned tisotumab vedotin doesn't need a biomarker. But if there are biomarkers that will annotate an ADC, that would be a process. But the point is, is that if we get earlier and earlier, where we start to get into curative intent – and I'm not saying that immunotherapy in the recurrent setting couldn't lead to a curative intent; it's just very unlikely. But if we get to the point where we're now developing the most effective strategies at primary treatment, that's where we have the opportunity to effect the greatest outcomes for our patients.

Dr. Moore:
Yeah, I totally agree.

Dr. Coleman:
So, Dr. Moore, we're sadly approaching the close of our conversation on cervical cancer. To wrap up, could you briefly list your key takeaways regarding the new and emerging data in cervical cancer?

Dr. Moore:
I think, just in general, key takeaways are, one, vaccines will prevent this. And you know, we have the example of Australia where they've eradicated cervical cancer and head and neck cancer. So just the opportunity to prevent cancer so we're not having to have this discussion globally would be the – I would just have to retire; I'd be so happy. So I think we always have to start with prevention as our main goal at all times.

My second key takeaway for this is cervical cancer doesn't always affect women with socioeconomic challenges, but it disproportionately impacts them. And so these new and novel therapies that we've been talking about are very exciting. And they do prolong life, but they're not equitably distributed in the United States. And they're certainly not equitably distributed globally.

Three is that I think drug development is working here. And we wouldn't need it if we could prevent this, but drug development is working; tisotumab is an example of that. And so I'm really grateful, honestly, for the interest of many pharmaceutical companies in cervical cancer.

And the next thing I would say, though, is biomarkers are very important. We can't waste resources. You know, I send next gen and IHC [immunohistochemistry] on every recurrent patient with ovarian and endometrial. Cervical cancer, you have to be a little bit more deliberate in what you send, but PD-L1 is essential. So adenocarcinomas are a little bit different. And so making sure that you know the HER2 status is really key, because you'll find it 30% to 40% of the time in some of the rare subtypes. And those patients can do incredibly well with some of our agents developed for breast cancer. And we can't forget that. It's not all an immune checkpoint inhibitor story here. So I think those would be kind of my top things.

Dr. Coleman:
Yeah, I think of course you took all my great ideas. But I do want to thank the pharmaceutical industry for giving this disease their attention. It has mattered. And it matters because those of you out there who are treating these patients are also putting them on clinical trials. So please, please, please support the development of these agents through clinical investigation. Well-designed clinical trials change the world.

So unfortunately, that's all the time we have today. So I wanted to thank our audience for listening and to thank you, Dr. Moore, for joining me and sharing all of your valuable insights. It was great speaking with you today.

Dr. Moore:
Thank you for having me. Always a pleasure.

Announcer:
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