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Immunotherapy Advances in Squamous Cell Anal Carcinoma: A New Standard of Care

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Incyte. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Here with me today to discuss challenges and advances in treating squamous cell carcinoma of the anal canal is Dr. Marwan Fakih. Not only is he a Professor in the Department of Medical Oncology and Therapeutics Research, but he's also the Judy and Bernard Briskin Distinguished Director of Clinical Research at City of Hope Comprehensive Cancer Center. Dr. Fakih, welcome to the program.

Dr. Fakih:
Thank you for having me. It's a pleasure to be here.

Dr. Turck:
Well, to start us off, Dr. Fakih, would you tell us about the history and current role of chemoradiation in localized squamous cell anal carcinoma treatment?

Dr. Fakih:
Yes. So anal cancer affects about 10,000 individuals a year in the United States, and it's rising in incidence. And it's important to think about, historically, the management of this disease. And when we evaluate a patient with anal squamous cell cancer, really, the first thing you want to do is stage that patient and understand, is this a localized cancer or metastatic?

Fortunately, the majority of cases present with localized disease. And the treatment for patients with localized anal squamous cell cancer is chemoradiation. And what we have learned over decades of work is that adding chemo to radiation improves the complete remission rate and reduces the chances of having a colostomy, particularly 5-FU.

And then we have learned further by adding mitomycin C in randomized trials of 5-FU mitomycin C versus 5-FU plus radiation that 5-FU mitomycin C radiation is superior. And that has established the Nigro protocol, or 5-FU mitomycin C and radiation, as the standard of care for localized disease.

Dr. Turck:
Now, what are some limitations and challenges clinicians might face when using chemoradiation in localized squamous cell anal carcinoma?

Dr. Fakih:
These are curative treatments. So anytime you are using curative therapy for cancer, you tend to accept certain toxicities. But I think the main thing to keep in mind is that when you combine 5-FU, mitomycin, and radiation, you may have significant bone marrow suppression, and these treatments can be quite harsh, especially on the elderly population. When you're dealing with individuals in their 70s or 80s, you can have a significant percentage of grade four leukopenia and neutropenia and a higher rate of infectious

complications. And in the frail elderly population, there's even some risk of mortality. And therefore, one has to take into account the performance status of the individual, the age, etc., in the decision-making, and sometimes switch more towards capecitabine and mitomycin C radiation therapy in that particular scenario, because capecitabine has less bone marrow-suppressing effects in the patients. So I think that would be one limitation—the toxicity.

The other limitation is that, frankly, these treatments do not necessarily individualize the risk to patients. So should you give a patient with T2 N0 squamous cell cancer of the anal canal the same dose of radiation and the same amount of chemotherapy as you do to someone who has T3 N2 squamous cell cancer of the anal canal? And I think there should be some additional effort placed in understanding if we can do some dose de-escalation in particular situations. So some data suggest that very, very early-stage disease, for example, may not need mitomycin C, although that's subgroup analyses from prior studies.

Dr. Turck:
And when it comes to metastatic disease, what gaps in care exist?

Dr. Fakih:
For metastatic disease, the gaps have been that we never really had level one evidence for any particular regimen in the management of patients with metastatic anal squamous cell cancer.

So historically speaking, we used to use 5-FU and cisplatin. And the use of 5-FU and cisplatin is really based on phase two clinical trials that have been associated with response rates of approximately 50 percent—those are some recent percentages—and sometimes of even complete responses. But all these patients will relapse, and short of any data from phase three settings, 5-FU cisplatin, historically, has been endorsed as the go-to regimen in the management of patients with squamous cell cancer of the anal canal.

Now, since then, we have also seen the development of carboplatin and paclitaxel in the management of patients with metastatic squamous cell cancer. And the adoption of that regimen has been largely based on a randomized phase two clinical trial that randomized patients to receive carboplatin and paclitaxel versus cisplatin and 5-FU. And this study showed that carboplatin and paclitaxel is safer than 5-FU cisplatin and was associated with more meaningful progression-free survival than cisplatin and 5-FU.

There was no statistical difference in overall survival, although there was a trend favoring carboplatin and paclitaxel. And based on that data, we and others, as well as NCCN, adopted carboplatin and paclitaxel in the management of metastatic squamous cell cancer of the anal canal.

But luckily now we see, based on the POD1UM-303 and level one evidence, that the field has moved forward. And now we have level one evidence that the standard of care should be carboplatin, paclitaxel, and retifanlimab, which is a PD-1 inhibitor.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Marwan Fakih about treating squamous cell carcinoma of the anal canal.

So Dr. Fakih, we were just talking about the current and evolving treatment landscape. As you were suggesting, the FDA recently approved retifanlimab in combination with carboplatin, paclitaxel for the first-line treatment of metastatic squamous cell anal carcinoma. Now it's the NCCN preferred regimen in this setting. So with all that being said, Dr. Fakih, would you tell us about the phase three data that led to this approval and guideline update?

Dr. Fakih:
Sure. So the POD1UM-303 is a randomized phase three clinical trial that completed accrual and reported on a first-line treatment of patients with metastatic squamous cell cancer of the anal canal or locally recurrent pelvic disease that is unresectable following chemoradiation.

And in that particular clinical trial, patients were randomized to receive either carboplatin and paclitaxel as a standard of care plus placebo, or carboplatin plus paclitaxel plus retifanlimab. And as we stated earlier, retifanlimab is a monoclonal antibody that targets PD-1. And the main idea here is to see if the addition of immunotherapy in the first-line setting would improve the overall survival, as well as the progression-free survival of patients with squamous cell cancer of the anal canal.

Now, this particular trial was a blinded, randomized clinical trial with a crossover design—meaning that the control arm that received placebo at the time of progression could be unblinded at that time and receive, in sequence, retifanlimab following progression.

To be noted here is that this is actually the first large phase three clinical trial that looks at an immunotherapy in the first-line setting. And this study enrolled 308 patients. The study was positive. It met its primary endpoint. The progression-free survival was superior in the patients who received carboplatin and paclitaxel plus retifanlimab versus carboplatin, paclitaxel, and placebo. The median progression-free survival improved by approximately two months—from 7.4 months to 9.3 months. And the hazard ratio was 0.63, which means that there was a 37 percent delay in the time of progression in the patients who received retifanlimab in addition to carboplatin and paclitaxel, compared to carboplatin and paclitaxel alone.

Now, despite the fact that this was a crossover design trial, and approximately half the patients did receive retifanlimab upon progression on the control arm, the median overall survival was numerically better in the carboplatin, paclitaxel, retifanlimab—29.2 months on the retifanlimab arm versus 23 months on the control arm. So this is quite exciting because we're seeing immediate improvement of about half a year in overall survival and a 37 percent delay in progression-free survival.

What I like about this study is that it also looked at the duration of response, and it shows that there's a subgroup of patients who have really very meaningful delay in time of progression, and that group of patients is quite a bit larger in the retifanlimab arm.

So adding a PD-1 inhibitor—namely retifanlimab—to carboplatin and paclitaxel improved the response rates by more than 10 percent. It went up from 44 percent to about 56 percent. And it also improved the complete response rates by eight percent. The patients who had complete response with chemotherapy alone—14 percent—went up to 22 percent. So roughly one in five patients had a complete response on carboplatin, paclitaxel, and retifanlimab.

And if you had a response, it appeared to be durable, because the median duration of response on the immunotherapy plus chemotherapy arm was 14 months. The median duration of response on the chemotherapy arm was half that, at seven months.

So I think this study is very conclusive. It tells us and shows us that we can delay progression. We can improve response rate. In patients who respond, the response is more durable. And that the addition of retifanlimab does result in a very strong trend improvement in overall survival, and that is despite the crossover. And that implicates the need of moving the PD-1 therapy—namely retifanlimab here—to the first-line setting, rather than in sequence.

Dr. Turck:
And now that we have combination therapy for first-line metastatic squamous cell anal carcinoma that includes an FDA-approved PD-1 targeting agent, how should oncologists approach patient selection and treatment sequencing?

Dr. Fakih:
I think now we have clearly a new standard of care. We have level one evidence that patients who present with metastatic disease should receive the POD1UM-303 regimen of carboplatin, paclitaxel, plus retifanlimab. That data is clear. The study met its primary endpoint. The adverse events were certainly acceptable and in line with any other PD-1 therapy.

And that same data applies to patients who have received chemoradiation for localized disease and subsequently had evidence of disease recurrence that is not amenable to surgical intervention for salvage, or who did not have a complete response and are still deemed not candidates for an APR surgical intervention for curative intent. So for those patients, the standard of care now is carboplatin, paclitaxel, and retifanlimab.

Dr. Turck:
Now, before we wrap up, Dr. Fakih, let's look ahead for just a moment. As the treatment landscape continues to evolve, what emerging strategies or investigational approaches are showing promise for patients with advanced or treatment-resistant disease?

Dr. Fakih:
You know, we have to look at additional strategies here. And there are some studies that are looking at different forms of immunotherapy. For example, can we leverage the HPV-related antigen presentation on squamous cell cancers with CAR-T therapy or with TCR therapies? Those are clearly intensive treatments, but if the endpoint is curative, they are certainly worth investigation.

Now that we have seen that adding PD-1 to chemotherapy in the first-line setting improves outcome, is there a role for other checkpoint inhibitors? Should those be in combination with carboplatin, paclitaxel, and retifanlimab? Are there other salvage strategies from combination immunotherapy in patients who progress on carboplatin, paclitaxel, plus retifanlimab? What is the role of antibody-drug conjugates in squamous cell cancers? There are certainly antibody-drug conjugates that are being evaluated within other squamous cell cancer tumors. What is the role of bispecific antibodies? So I think these are the things that we should be looking at in the near and intermediate future.

Dr. Turck:
Well, as those forward-looking thoughts bring us to the end of today's program, I want to thank my guest, Dr. Marwan Fakih, for joining me to discuss the treatment landscape for squamous cell carcinoma of the anal canal. Dr. Fakih, it was great having you on the program.

Dr. Fakih:
Thank you for having me.

Announcer:
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