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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Guideline Updates Redefining Squamous Cell Carcinoma of the Anal Canal 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 the updated NCCN® Clinical Practice Guidelines for the management of advanced squamous cell carcinoma of the anal canal is Dr. Aparna Parikh. Not only is she an Associate Professor in the Department of Medicine at Harvard Medical School, but she's also the Program Director in GI Oncology at the Mass General Brigham Cancer Institute. Dr. Parikh, welcome to the program.

Dr. Parikh:
Thanks so much for having me.

Dr. Turck:
Well, let's start with the big picture, Dr. Parikh. The latest NCCN® guidelines now frame immunotherapy as part of the preferred first-line treatment for unresectable, locally advanced, or metastatic squamous cell carcinoma of the anal canal, rather than reserving it for later lines. From your perspective, how does this update change the way you set expectations with patients at the time of diagnosis?

Dr. Parikh:
Yeah, I think this has been a really exciting update for patients, and it's really great to now have an immunotherapy option to add to our toolbox of treatments for patients living with anal cancer. So taking a step back, I think anal cancer is still a fairly rare cancer; it's only about 2 to 3 percent of all GI cancers. That being said, we have seen in the United States, in particular, a steady increase over the last several decades. So we're seeing more of these patients. We see patients with presentation of metastatic disease, increasingly so. So it's really great to have additional options for patients that have metastatic disease.

Historically, for decades, guideline-based first-line therapy has been cytotoxic doublets; carboplatin and paclitaxel has been the standard of care for decades. And that was really based on randomized data from a pivotal study called the InterAACT study, which showed a promising response rate—good PFS and median OS—in chemo-naive patients. And that was shown to be better and more tolerable than cisplatin and 5-FU. So in the curative setting for anal cancer patients, we use 5-FU plus mitomycin as the definitive treatment for those patients, and the chemotherapy is a great option for patients.

But we knew that we needed to do better. And prior to this last year, immunotherapy was reserved as monotherapy in the second-line setting with modest activity for patients after carboplatin and paclitaxel-based chemotherapy. And with randomized data using the standard InterAACT backbone with carboplatin-paclitaxel compared to carboplatin-paclitaxel with a PD-1 inhibitor, we now had a positive study for PFS, which has really changed the landscape of how we think about patients with metastatic anal cancer and using PD-1 combination therapy with carboplatin-paclitaxel no longer as second-line monotherapy.

Dr. Turck:
Now as you were just discussing, if we look more closely at this update, a PD-1 inhibitor combined with carboplatin and paclitaxel is the preferred first-line option based on phase 3 data showing improvements in progression-free survival and overall survival rates. So with that in mind, what aspects of the phase 3 evidence do you think were most influential in informing this update?

Dr. Parikh:
In immunotherapy, it's beyond just overall response rates, so the PFS. But what you see that is really compelling when you looked at the

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tail of the curves is that you have patients that are surviving with their anal cancer for substantial periods of time. So what it showed to us was there's a subgroup of patients that were deriving prolonged benefit with the addition of immunotherapy. This is consistent with what you've seen with the addition of immunotherapy to other cancer types too. So yes, we have randomized data showing improvement of PFS. But I think what was really notable was the duration of benefit and the tail of the survival curves.

I think the other piece that is important to note is that the benefit was consistent across predefined subgroups. So there was no need to select for PD-L1 status, for example. So this is really an all-comer patient population; typically not in all patients, but it's primarily an HPV-driven cancer with squamous histology. I think we do see rare anal adenocarcinomas. I think it's really important to note for the audience that this is typical anal squamous cell carcinoma, not the rare anal adenocarcinomas. And then that benefit with the PD-1 combination therapy across all predefined subgroups is a really important point.

Dr. Turck:
So as you were just saying, the updated guidelines also note the perhaps surprising observation that there's a benefit with chemoimmunotherapy regardless of PD-L1 status. How does that observation influence treatment decision-making in routine practice?

Dr. Parikh:
Yeah, so I think really for the far majority of patients, carboplatin-paclitaxel plus PD-1 antibody is where we turn to. I think there are rare patients where there may be strong contraindications to immunotherapy. I know I'm a little bit privileged to work with a group of subspecialists that can handle pretty severe immunologic toxicity as well and help me manage patients who may have preexisting autoimmune conditions. And we're not talking about CTLA-4; we're talking about PD-1 monotherapy in addition to chemotherapy. And so with PD-1 alone, we know that toxicity rates are lower too. So I would say for the far majority of patients, unless there is a true contraindication to immunotherapy, we are using that triplet of carboplatin-paclitaxel with PD-1.

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. Aparna Parikh about the updated NCCN® clinical practice guidelines for the management of advanced squamous cell carcinoma of the anal canal.

So, Dr. Parikh, now that we've talked about how the NCCN® updates redefine first-line treatment expectations, let's shift to what these changes mean across the rest of the disease course. Given that single-agent PD-1 inhibitors are still recommended after platinum-based chemotherapy, how are you thinking about sequencing now that immunotherapy may be introduced earlier in the disease course?

Dr. Parikh:
Once this data was presented well over a year ago, I had patients that were already on carboplatin-paclitaxel, and I very quickly went ahead and added it in at the time of approval for patients that were already in their induction phase of chemotherapy. For patients that have already been exposed to carboplatin-paclitaxel and completed their induction phase, I think it's a conversation with the patients around when the right time is to introduce the immunotherapy. I think standard second line is a completely appropriate option. But many patients with metastatic anal cancer might have oligometastatic progression, for example. Then you do some local therapy to give them a break from their first-line chemotherapy. And then at the time of reintroduction, you might do it with carboplatin-paclitaxel and PD-1 again. So it really is a case-by-case basis of who is truly second-line IO naive. I think you want to give them IO versus those who may have not progressed necessarily on first-line therapy and you're thinking about the addition, so I think it's a little bit hard to generalize. I think we changed this in our own institutional pathways over the last summer.

So I think it's really exciting for patients, but we do have to think about it on a case-by-case basis of where they are. But again, in the guidelines, I think PD-1 monotherapy is still standard after progression of platinum-based therapy; I think in the guidelines, it's after progression. So again, some patients may have just taken a break and not progressed, and then you think about what you want to do at the time of reintroduction of chemotherapy. So it's a little bit different based on whether you progressed or are on a chemo holiday, for example.

Dr. Turck:
Now beyond regimen selection, the NCCN® guidance highlights factors, such as performance status, autoimmune comorbidities, HIV status, and prior pelvic radiation. When considering systemic therapy, what kind of impact do these considerations have on your treatment decisions?

Dr. Parikh:
So I think in terms of performance status, carboplatin-paclitaxel generally can be quite well managed. I think on the spectrum of chemotherapy that we give in GI malignancies, especially with some dose adjustments, I think you can get people through quite well. You might have to adjust doses a little bit for counts over the six months of carboplatin-paclitaxel treatment. Some patients can get

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neuropathy, but in general, I think even for elderly patients, it's pretty well tolerated. Again, you might do some dose modifications, and renal function may impact that.

Patients living with well-controlled HIV viral load were allowed in the pivotal study, so it doesn't impact treatment there. I think patients can get immunotherapy if they're living with HIV and have well-controlled viral loads.

For autoimmune conditions, it really depends on the nature of autoimmune diseases. With mild rheumatoid arthritis, for example, maybe you can get them by without too much difficulty. I've had patients with autoimmune GI conditions where I've worked with our GI colleagues to introduce PD-1 monotherapy. In some patients, we've been able to avoid flares, and in others we've had to look at biologics and steroids to get us through. So again, I would say for the far majority of patients, if they're chemo-eligible, I think you feel very comfortable giving IO.

Dr. Turck:
Well, we've certainly covered a lot today, Dr. Parikh, and as clinicians consider the updated recommendations in the evolving evidence showing the potential for more durable disease control, what key takeaways should guide their current treatment approach?

Dr. Parikh:
I think the current takeaways are that unlike other tumor types, no biomarker selection is needed for the use of PD-1 monotherapy with chemotherapy in patients with metastatic anal cancer. These are patients where you don't really see a lot of biomarkers if you do NGS testing anyway.

And so for many of these patients—again, we see this with patients with HIV—you should not withhold therapy because of that. So really, I think the easy indication is to give PD-1 with chemotherapy, and it's a chemotherapy background that people are very comfortable with and has been the gold standard of treatment for years. And people are very comfortable now with PD-1, so it's a well-tolerated regimen and a good option for patients that can substantially improve outcomes for these patients. So I think that's my take-home message.

Dr. Turck:
As those forward-looking comments bring us to the end of today's program, I want to thank my guest, Dr. Aparna Parikh, for joining me to review the updated NCCN® Clinical Practice Guidelines for the management of advanced squamous cell carcinoma of the anal canal. Dr. Parikh, it was wonderful having you on the program.

Dr. Parikh:
Thanks for having me.

Announcer:
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