Rare Forms of Bladder Cancer: Question and Answers

Stephanie C.: Yes. Thank you so much, Dr. Apolo. This is incredibly informative. And we do have a number of questions. So, one of the participants asked, "I have a periodic diagnosis of nested variant cells, non-muscle-invasive. Is this small cell or something else? What is recommended for treatment?"

Dr. Apolo: Well, nested cell is another really, really rare, rare variant of urothelial carcinoma. And we don't know the best management for these tumors. So, right now we manage them as urothelial carcinoma, depending on what stage it is. So it's non-muscle-invasive. So, these tumors are managed locally, and when they become invasive, sometimes they declare themselves and they transform. And it's not uncommon to have multiple cell types that are together. And really what we do is we take the most aggressive cell type and we treat that one, if we know how to treat them, if the treatment is different than urothelial carcinoma. But unfortunately for nested variant, we treat it as urothelial carcinoma, but although we do know it behaves more aggressively.

Stephanie C.: Thank you. Okay. "Are micropapillary tumors chemo-sensitive?"

Dr. Apolo: This is a great question. And this is a common issue that comes up. If somebody has muscle-invasive bladder cancer with micropapillary, do we give them chemotherapy? The argument is these may be more resistant to chemotherapy, and that these patients should go straight to cystectomy. But another argument that is made is that these patients often have lymph node metastases already, and they have a higher rate of spread. So, wouldn't it be better to try to treat the systemically as metastatic disease initially, with chemotherapy, and then do

the cystectomy later. So, some theories have shown that micropapillary may be more resistant to chemotherapy, but some theories have shown that it may not be. So, it's still controversial as to what the best management... Especially for muscle-invasive disease, where the treatment is remove the bladder and give chemotherapy or not give chemotherapy, the management is controversial. And that's why I didn't put it in my slide because some retrospective reviews have shown that yes, these tumors are more resistant. But then some other retrospective reviews have shown that these tumors do better with chemotherapy and surgery than just with surgery alone. And again, these are small. So it's really hard to interpret it because sometimes you need really large numbers to tell the differences between whether there's a benefit in adding a treatment or not. But I say, until we know otherwise, I think it's appropriate to treat them with chemotherapy. And if they're muscle-invasive disease, with a radical surgery afterwards.

Stephanie C.: Okay, thank you so much. I have a question. I think what this individual is asking is, "How often is precise delivery of treatment? Are the different types of drugs delivered precisely to cancer cells in these rarer forms of disease. I know that within all variant of the common variant, when we have a specific genomic mutation, they can target specific things. Do they know enough about these rare cancers to be able to target therapies?"

Dr. Apolo: Not yet. No, and urothelial carcinoma, regular bladder cancer just received the first targeted therapy approval by the FDA this year. So, we're really just learning enough about bladder cancer, and that was an FGFR3 inhibitor, that's now approved for urothelial carcinoma that has FGFR3 mutations or alterations. We don't know enough about how to target these rare tumors, rare histologies, or variants enough to treat them like a personalized approach, by their mutational, by their genetics, yet. Some tumor types we know enough to treat them by targeting the mutations. Bladder cancer, we just have the first approval this year. But for the rare variants, we do not yet.

Stephanie C.: Well I think you did an amazing job of highlighting some of these challenges, particularly in really understanding some of these very rare variants of bladder cancer. What is your recommendation then for patients who have a diagnosis of one of these off-the-beaten-path types of bladder cancer. Should they engage in a clinical trial, is there anybody that's doing any work to do a deeper dive collectively across the board? Maybe, a tumor registry or something that's looking at these different non-common variants of bladder cancer. Is there anything you can suggest to patients?

Dr. Apolo: So, I say it's always good that if you have a diagnosis that is uncommon, to get an opinion from a high-volume academic center where the investigator or the doctor has experience with these rare tumors. And there are many, many investigators throughout the country that work in bladder cancer and are interested in rare bladder tumors and variant histologies, and are collecting tumors, and are doing RNA-sequencing on them in order to learn a little bit

more about the biology of these rare tumors. So, find an investigator near you that can advise you on your management.

Dr. Apolo: And if it's not possible for you to travel, ask your doctor to find an investigator that they can talk to, run the case by. So, at least your doctor engages an expert in your management if you can't travel there. But I think it's always better for you to go and get a second opinion from a high-volume center if you can because these tumors are rare and every case is different. So, I can only kind of give an overview of how they're generally managed. And for most urothelial carcinoma, variants are generally managed as bladder cancer, it's just regular urothelial cancers. But for the pure histologies, these are managed differently. So I think it's important to kind of have another pair of eyes that has knowledge with these tumors to discuss your case. So, number one, I'd say we're going there, but if it's not possible to travel there, at least have your doctor engage an expert by contacting them, getting a review on the pathology. That's another thing too, is the pathology. Your tumor's being looked at under the microscope by a pathologist. And sometimes just a pathologist hasn't seen many of these rare tumors. They may not be as familiar in making the diagnosis. So, when you get a second opinion, you often also get a pathology review by the pathologist in the academic center that can confirm or not confirm the diagnosis that was made of the rare tumor.

Stephanie C.: Great. Thank you so much. "Are there any particular tests that are used to diagnose the existent micropapillary carcinoma? Or is it just the pathology that determines that?"

Dr. Apolo: So, it's morphology. So what I mean by that is, it's what it looks like under the microscope. And that's generally the way that it's doing... And there's sustain too, but generally it's by morphology. So again, it's subjective, and that's why the diagnosis of these tumors are increasing as pathologists are becoming more aware of this subtype and are diagnosing it more and more, as they learn more as to how to do it.

Stephanie C.: Okay. Great. I know you can't answer specific questions. But there is one that came in, "What is your opinion about the potential use of enfortumab for rare forms of bladder cancer? To my understanding, it's pending at the FDA for approval for use with lung and bladder cancer. It's been diagnosed as a potential for my father's small cell bladder cancer if approved for rare forms. What is your opinion?"

Dr. Apolo: It's a great question. I think that's a really good question. So, enfortumab vedotin is a new drug. It's a new drug that is showing promise in regular urothelial carcinoma bladder cancers, an antibody-drug conjugate. And what it basically is, it's a fancy chemotherapy that is carried by an antibody, specifically against a specific antigen that is Nectin. When Nectin is found in over 90% of urothelial carcinomas, whether Nectin, which is the antibody target, is found in small cell bladder cancer or whether it's found in adenocarcinoma, urachal, I

don't know the answer to that. I mean, I think that that we need to find out. I mean, how commonly is Nectin expressed? And if it is, can we give this novel drug to non-urothelial carcinoma tumors?

Dr. Apolo: I mean, I think that's an excellent question. And I don't know the answer to that, and I think we need to find out because once these therapies are approved for urothelial carcinoma, why not make it... Especially if there's limited treatment options. If somebody tells you, "There's nothing else I can do for you," why not try something new and learn from it? So of course, it should be done ideally in the controlled setting of a clinical trial, but that's going to be tough. And I don't know if the company has any trials ongoing with variant histologies or rare tumors.

Dr. Apolo: But, that's a terrific question, and I think you give the standard chemotherapy. And now we know that immunotherapy in combination with the chemotherapy is active for small cell. But once that stops working, it would be ideal to try a novel therapy. And if, I guess, the insurance approves it or if there's a way of getting a novel therapy, I think it's reasonable to try something new. But really it's important to know whether small cell has that antigen, and I don't know the answer to that.

Stephanie C.: Okay, thank you so much. "In patients with mixed histology in their primary tumors, do metastases retain the same proportion of variant cells or do the more aggressive cell types metastasize selectively?"

Dr. Apolo: These are really, really good questions. And I'm really I'm pressed with how knowledgeable the audience is. So, we don't know, but it looks like generally the more aggressive cell types that are resistant to the treatment that is being given, are the ones that grow. Often we get something called a mixed response. Some tumors shrink and some tumors in other parts grow. And it's generally the more aggressive cell types that grow. And in general, bladder tumors are very mixed. So, it's the more aggressive components that eventually become metastatic. Sometimes when you biopsy tumors, they no longer say urothelial carcinoma. All they'll say is poorly differentiated carcinoma. They don't even say urothelial... And they'll look something like more consistent with urothelial carcinoma because they know the patient has bladder cancer, but most of the time they differentiate so much because they're growing so quickly, they no longer hold the morphology or the appearance of the initial tumor.

Stephanie C.: Interesting. Thank you so much for that explanation. I have one more question. We have time for one more question. And the participant wanted to know if you were familiar with any links between bladder cancer and spina bifida, especially situations of reconstructive bladder in patients.

Dr. Apolo: So, there has been some trials looking at specifically patients with indwelling catheter, spinal cord injury to kind of... These are retrospective, just to see the incidence of bladder cancer. And some of these are inconclusive and some of

them say, "Yeah, they look like there is a link." With patients that are paraplegic or... Not specifically spina bifida, but that have a spinal cord injury, and either catheterize themselves or have indwelling catheters. And patients that have had reconstructions too, like the ureter reimplanted or certain surgeries within the urothelial tract. So there is a small retrospective association that has been reported, but inconsistently.

Stephanie C.: Okay. Well, thank you very much. This has been very enlightening. And I hope that for the people that have been on this webinar, they really learned a lot about what's being done and what still needs to be done about rare forms of bladder cancer. They do exist. So I really do appreciate it. I'd like to again thank our sponsors, Astella SeattleGenetics, Bristol-Myers Squibb, EMD Serono Pfizer, Genentech, Janssen, Merck, and Photocure for their support of our webinar programs. Remember that we will be recording and providing a transcript online, but you will get a link to the unedited recording of tonight's program, tomorrow. And you will also receive an email that's going to ask you to complete a few short questions. Your opinions about this program are very important, and we do appreciate your joining with us tonight. We look forward to seeing you on future webinars. Thank you so much Dr. Apolo.