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Rethinking the Endometrial Cancer Treatment Paradigm

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

Dr. Turck:
This is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and here to help us rethink the endometrial cancer treatment paradigm are Drs. Susana Campos and Richard Penson. Dr. Campos is an Assistant Professor of Medicine and the Director of Educational Activities at the Dana Farber Cancer Institute at Harvard Medical School in Boston, Massachusetts. Dr. Campos, thanks for being here today.

Dr. Campos:
Thanks for having me.

Dr. Turck:
And Dr. Penson is the Clinical Director of Medical GYN Oncology at Massachusetts General Hospital in Boston. Dr. Penson, it's great to have you with us.

Dr. Penson:
Great to be here. Thank you.

Dr. Turck:
To start us off, Dr. Campos, would you tell us about the treatment options currently available for endometrial cancer, and if they have any limitations?

Dr. Campos:
Sure, absolutely. So, there are various treatment options. And there are surgical options. There are radiation oncology options. But, of course, as a medical oncologist, I'm most excited about some of the new systemic options. And those can be anything from hormonal manipulation, combinations of hormonal manipulation with PI3 kinases, combination of hormonal therapy with CDK4/6 inhibitors.

And of course, what's come on the scene in the last several years, and which we're going to hear a little bit more about in a couple of weeks, is the role of immunotherapy. At present, we have these checkpoint inhibitors approved in patients who have had prior systemic therapy. And what I'm hoping is that we're going to hear some very favorable data in the next couple of weeks at the SGO meeting, based on some studies called the RUBY-1 and the NRG-018, looking at whether immunotherapy improves progression-free survival and overall survival. In earlier stage patients, for example, stage III, IV, and of course, recurrent. So, there is tremendous wealth in terms of clinical trials and different options for patients with uterine cancer. In terms of limitations, there are always limitations. I think what we've learned over the past couple years is that endometrial cancer is not by just one cancer, it's made up by many different elements. And those elements really lie in the genomics of the cancer. And what we learned is that even some early-stage uterine cancers can be quite virulent. And other times, these early stages can appear virulent morphologically, but they are not. Actually, they have a better prognosis.

So, I think some of the limitations are getting genomics up and running very early so we can make treatment decisions, whether they be escalation or de-escalation in treatment in these early-stage risk patients. I think that would actually help patients very much. We don't want to overtreat people. We don't want to undertreat people.

Dr. Turck:

Well, as a quick follow-up to that, Dr. Campos how have some of the limitations you discussed contributed to unmet needs for our patients?

Dr. Campos:
I think, in a way, we perhaps overtreated some individuals. You know, and in some cases, we've undertreated some individuals. So, I think that it's now with this information at hand and with our knowledge of genomics increasing quite quickly, I think we're going to be able to better delegate treatment. I think the limitations have been not necessarily giving the right treatment, the necessary treatment based on information we didn't have many years ago. But with this limitation and erasing this limitation, we're going to be really able to tailor the treatment to the patient, the morphology of this disease, but more importantly, the genomics of this disease.

Dr. Turck:
Turning to you now, Dr. Penson, what are some emerging treatment modalities for advanced or recurrent endometrial cancer?

Dr. Penson:
So as Sue said, this is an area where there's been a huge change with a better understanding of the of the molecular underpinnings of disease really defining our treatments. So for advanced or recurrent disease, the hot topic is immunotherapy. And so, at the moment, we really divide that up between the KEYNOTE-775 lenvatinib and pembrolizumab option for patients who have microsatellite stable tumors. And then the tumors that have microsatellite instability high characteristics they are mismatch repair deficient, the single agent pembrolizumab or one of the other options like dostarlimab can have amazing efficacy. So the molecular for most of us in clinical practice immunohistochemistry of the mismatch repair proteins is really picks out a population where we completely change what we do. We are able to drop lenvatinib, and with less side effects, get way better options. I mean in Dave O'Malley's study it was 68 percent of people had not had progression of their disease in the group who responded I think two years later, it was just amazing.

So that's also true of some of these sorts of aggressive subtypes like HER2 neu driven disease when we add trastuzumab, it again, it impacts time to recurrence and overall survival.

And what Sue was hinting at is that the new targets going beyond HER2, the DNA damage response targets for the serous tumors lots of new targets in terms of how we expand how we think about hormonal therapy, which we maybe should touch on in a moment.

But immunotherapy is really at the top of the pile of exciting things. And I think it's true to say that endometrial cancer stands out as the archetype before being able to expand the number of patients who get access to the therapy. Normally a select few, like the 20 percent of melanoma patients who get a miracle cure. To be able to add lenvatinib in everybody with recurrent endometrial cancer get immunotherapy as second-line therapy really changed the paradigm of treatment.

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. Susana Campos and Richard Penson about the treatment landscape for endometrial cancer.

So now that we know more about the treatment options available for endometrial cancer, let's take a look at them in action. Dr. Campos, how might we select a treatment that takes both tumor characteristics and patient attributes into account?

Dr. Campos:
Well, that's a very important question because you do really want to align both of those elements. In terms of tumor characteristics, I mean, depending on the type of tumor it is, the histology, perhaps the molecular profile, you propose a treatment to the patient. But equally important is to understand what the patient's comorbidities may be. The patient may have hypertension, diabetes, they may have a poor performance status. And even though those tumor characteristics suggest a certain treatment, they don't necessarily align with the physical wellbeing of the individual. So that's actually quite important.

It's also important to engage with the patient like and how it's going to affect the quality of their lives. And so that is an open discussion with a patient. So, you propose a treatment, you try to balance the treatment with what we know the patient to have in terms of comorbidities and you engage in a dialogue that hopefully makes the best decision for that individual.

Dr. Turck:
And from your vantage point, Dr. Penson, how might we incorporate patient-centered care models into our approach?

Dr. Penson:
So, we often think of the patient-centered care as around the tumor. So, there is a fabulous study that's being run in Canada and Europe that uses the Cancer Genome Atlas subtypes of endometrial cancer it's called the RAINBOW trial. So red is p53 mutant where olaparib is being included as part of the therapy. The green is mismatch repair deficient, and the interest is in immunotherapy, durvalumab in that trial. Orange, hormonal therapy where we are revisiting treatments that 60 or 70 years ago looked promising, the progestins. Could two

years of that make a difference adjuvantly with chemoradiation therapy for high-risk early-stage cancer? And then POLE is where de-escalating treatment where you almost certainly don't need any extra treatment beyond surgery is the fourth category. And so that's like tumor characteristics.

When it comes to patient characteristics, I think the Vicky Makker's KEYNOTE-775 trial is just the perfect example of that. There is a brilliant review by her in The Oncologist which really outlines when patients get toxicities. And so lenvatinib, which is quite a tough drug, is a drug that we really have to tailor by dose to the patient experience. In the phase 2 as an effective single agent, it was a 24-milligram dose, in Vicky's study 20 milligrams. And I commonly will start patients who are a bit more vulnerable at 14 milligrams. Just this week, dose-reduced somebody from 10 to 8 milligrams, and they're doing well. Getting that dose right, and hypertension takes off about three days after you start the dose. So being able to proactively and reactively tailor the treatment perfectly to the patient, I think there's is almost no better example than the careful use of lenvatinib in endometrial cancer.

Dr. Turck:
Now, before we close, I'll pose the same question to you, Dr. Campos, what strategies could help us take a patient-centered approach to advanced endometrial cancer care?

Dr. Campos:
I think in very much the way that Dr. Penson has alluded to, is understanding the genomics of the actual cancer, and tailoring the therapy to that individual. But we're starting to look at whether it be an early-risk, early-stage high-risk uterine cancer, you know, who do we treat? Who do we have to treat individuals and who do we don't treat? So, can we escalate? Do we have to escalate the treatment? Can we de-escalate the treatment, as Dr. Penson was saying, in these patients who might have a specific genomic signature called the POLE mutation?

And you know, into that light too, when you do in essence, engage in it form of treatment with the individual, I'm going to pick the concept of immunotherapy. Immunotherapy is in the most amazing component of what we do every single day. And you can have magical responses, but you also can have significant toxicities of any grades. And so, it's so very important to actually think about the patient and think about what their comorbidities are their other illnesses, and when you take into account the choices that you make for the therapy.

But one thing that I've learned over the years that's exceptionally important is to bring the patient into the fold. They must engage in terms of it's not just showing up every three weeks and reporting your symptoms. It's reporting your symptoms, any toxicities that may have come from these medications as early as possible so that the clinician can mitigate those toxicities. When you mitigate these toxicities, individuals are more likely to stay on therapy than they are to abort them. And in that end, they will also benefit from the treatment. So, I think it really is about engaging the patient in the care of themselves.

Dr. Turck:
Well, with those final tips in mind, I want to thank my guests, doctors Susana Campos and Richard Penson, for joining me to discuss the management of advanced or recurrent endometrial cancer. Dr. Campos and Dr. Penson, it was great having you both on the program.

Dr. Campos:
Thank you.

Dr. Penson:
Thank you.

Announcer:
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