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The Hidden Toll: Recognizing the Treatment Burden of mCRC

Announcer:

You're listening to *Project Oncology* on ReachMD. Here's your host, Dr. Charles Turck.

Dr. Turck:

Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss the challenges associated with the treatment of refractory metastatic colorectal cancer, or mCRC for short, are Drs. Richard Kim and Benjamin Weinberg. Dr. Kim is a Service Chief of Medical Gastrointestinal Oncology and Senior Member in the Gastrointestinal Oncology Department at Moffitt Cancer Center in Tampa, Florida. He's also a Professor of Oncology at the University of South Florida College of Medicine. Dr. Kim, thanks for being here today.

Dr. Kim:

Thank you for having me. Appreciate it.

Dr. Turck:

And Dr. Weinberg is an Associate Professor of Medicine and Attending Physician specializing in Gastrointestinal Medical Oncology and Sarcoma at MedStar Health in Washington, DC. Dr. Weinberg, it's great to have you with us as well.

Dr. Weinberg:

Thank you so much.

Dr. Turck:

Let's jump right in starting with you, Dr. Weinberg. What are the current unmet needs among patients with refractory mCRC?

Dr. Weinberg:

Right, so colon cancer, a very common cancer, unfortunately, very common cause of cancer-associated death in the United States. If you take patients who have metastatic disease at the time of diagnosis, only about 14 percent are alive five years later. And likely, those few patients are patients who can undergo potentially curative surgeries from the sites of metastatic disease—be it in the liver or lung, for example.

We only have basically two lines of standard chemotherapy, and then a variety of drugs on the third-line setting. So clearly, there's a huge unmet need for patients in terms of new drugs, more effective drugs, less toxic drugs, in order to improve survival. So unfortunately, we only have a handful of drugs at our disposal for this very common illness. And we're desperately trying to find new, more exciting, and targeted therapies and trying to make immunotherapies work for this patient population, which historically has not benefited from the immunotherapy revolution to date.

Dr. Turck:

And turning to you, Dr. Kim, would you tell us about the challenges that occur based on those unmet needs?

Dr. Kim:

Yes, I think as Dr. Weinberg mentioned, I think the key here unmet need is we need better biomarkers, for example. We know that, I think the biomarker testing is a must for anybody with advanced colorectal cancers because it will determine what kind of aberration a patient may have; therefore, we have a plan for that patient. However, we could definitely improve on that because there are certain biomarkers that we have, for example for immunotherapy, that only applies for five percent of the patient and that those are MMR status, MMR deficient patient or MSI high patients. Those are the patients that truly benefit from immunotherapy. But in 2023, however, there

are trials conducting with immunotherapy in patients who are MMR proficient or microsatellite stable, and we know even those patients, that some patients do respond, but exactly at this time, we don't know which of those patients are. Therefore, I think having a better biomarker testing to determine which patients will exactly benefit from the immunotherapy is an unmet need.

Second thing that's unmet need is that based on all the targeted drug that's currently out there, such as a BRAF, HER2, for example, KRAS, we need to better understand the resistant mechanism. Unfortunately, these patients, even though those drugs may work at the beginning, they all develop resistance, and if you could better understand the resistant mechanism, we could potentially overcome them.

Dr. Turck:

Now coming back to Dr. Weinberg, let's turn our attention to the treatment landscape. What therapies are currently available for patients?

Dr. Weinberg:

Right, so very briefly, in the frontline setting, it's typically chemotherapy doublet or triplet with the biologics, such as FOLFOX, FOLFIRI, FOLFOX/FIRI, often given with drugs that target VEGF, such as bevacizumab or drugs that target the EGFR pathway, such as cetuximab or panitumumab. We know that patients with left-sided RAS wild-type tumors really seem to benefit preferentially from anti-EGFR drugs. And there's a lot of data now out there to support that. We are now getting smarter, as Dr. Kim mentioned, in terms of broader biomarker testing, so not just KRAS, but looking at things like BRAF, HER2, other potential markers of de novo resistance to anti-EGFR drugs, either in tissue testing or liquid biopsy type testing, where we may be able to predict who's really going to benefit from anti-EGFR therapy with chemo in the frontline setting, left-sided or right-sided primary tumor.

And then we now have BRAF targeted therapies for patients with BRAF V600E mutated metastatic colorectal cancer in the second line and beyond setting with encorafenib with an EGFR drug, cetuximab or panitumumab. We now have HER2 targeted therapies with tucatinib/trastuzumab that was recently FDA approved. But outside of these targeted therapies and rare things like NTRK fusions in the third line, we have drugs that have limited efficacy and toxicity that is real. So those are drugs like trifluridine/tipiracil, which is an oral fluoropyrimidine, basically pill chemotherapy, as well as regorafenib, which is a poly tyrosine kinase inhibitor. But data from the SUNLIGHT trial, adding bevacizumab to trifluridine/tipiracil, seems to be superior to trifluridine/tipiracil monotherapy. So that's probably going to be the preferred third line regimen followed by regorafenib. And then the next kid on the block looks to be fruquintinib, which has some similarities to regorafenib, which may be a fifth-line drug.

So that's what we have so far. And again, these third-line drugs have, again, very limited response rates, definitely real toxicity. So these are patients where we're always looking to find novel targeted therapies and enroll them in clinical trials. A lot of what the work I do is in early phase clinical trials for refractory metastatic colorectal cancer.

Dr. Turck:

And as a follow-up to that, Dr. Weinberg, what challenges are associated with those treatment options?

Dr. Weinberg:

Right, so again, trifluridine/tipiracil is an oral chemo, so a lot of myelosuppression, a lot of GI toxicity—regorafenib, if dosed at the FDA label, 160 milligrams daily for three weeks, is very difficult for patients to tolerate from fatigue, other GI side effects, hand/foot skin reactions, so they have real toxicities. And again, they're singles, they're not homeruns that they can keep patients' disease stable for months, but usually not many months. And again, with toxicities, I view them more as a bridge, as a stepping stone, to get on to a clinical trial or some sort of local therapy.

And then the group that we haven't mentioned much of is the rare, the four to five percent that is MSI high, that really does benefit from immune therapy. But even in that group, in the KEYNOTE-177 study, pembrolizumab versus chemo, about a third of patients had disease progression as their best response to immunotherapy. So clearly even in that population, we need to figure out who's going to really benefit from immunotherapy or who may need doublet immunotherapy and who may really need chemotherapy. So there's a lot that we're still trying to figure out.

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 Drs. Richard Kim and Benjamin Weinberg about the treatment challenges in refractory metastatic colorectal cancer care.

So, Dr. Kim, now that we have a better understanding of the treatments presently available for mCRC, let's look ahead for just a moment. What novel therapies are on the horizon that might help us address the challenges Dr. Weinberg spoke about earlier?

Dr. Kim:

Sure, I think in a refractory setting, as Dr. Weinberg mentioned, there are a lot of drugs that's out there. I mean, we just don't understand at this time how to sequence them at this time. That's one area. But however, in terms of the novel drugs that's currently being out there, the hot area right now is, once again, is trying to convert this, what we call a cold tumor. These are MMR proficient tumor, microsatellite stable tumors, to add more of a hot tumor by combining immunotherapy with some other drugs. And I think right now, that's the area that's in focus right now.

And there has been a lot of data out there that's already been presented and more to come. For example, can you combine immunotherapy with a TKI? Can you combine immunotherapy with chemotherapy and monoclonal antibody? Or can you combine immunotherapy with another immunotherapy? So those are the ongoing trials right now at this time. Now there are some results that has been released. For example, combining PD-1 with a CTLA4 inhibitor, second-generation CTLA4 inhibitor, showing very high response rate in an early study. So based on that, the plan is to do a larger phase 3 study; however, the efficacy was just confined to patient with non-liver mets, interestingly enough. And there was a lot of hype about using a combination of pembrolizumab and lenvatinib based on phase 1/phase 2 studies showing very high response rate. Now phase 3 study was done, and that's being presented at GI ESMO in two weeks. However, there was a press release that came out saying that the trial did not meet its endpoint.

So there are some negative studies and some positive studies ongoing right now. So we have to wait to see how those results will read out. But I think that's probably the most exciting area that we're trying to look for to see is can we convert this cold tumor to a hot tumor by adding another drug to immunotherapy?

Another area, it's not a novel therapy, but we're moving towards is that trying to use this targeted therapy, whether it's anti-HER2 agents or whether it's anti-BRAF agents in the first line. We know those agents are currently approved in refractory setting. Question is—can you move it up the first line with chemotherapy to improve the outcome and, hopefully, make a huge impact in overall survival in those patients?

Dr. Turck:

Lastly, I'd like to hear some closing thoughts from each of you. Starting with you, Dr. Weinberg, any final takeaways you'd like to leave with our audience today?

Dr. Weinberg:

Right, so building on what Dr. Kim was just saying, we've been frustrated and trying to throw different immunotherapy combinations, immunotherapy TKI, immunotherapy chemo combinations, which so far have not yielded any real fruit for our patients. And I think we're finally starting to get there by finding the right combinations, but also finding the right patients. So we know that the 96 percent of patients with microsatellite stable colorectal cancer are diverse, a heterogeneous population, some of which based on AtezoTRIBE data just presented at the ASCO Annual Meeting 2023 a couple weeks ago. We know that there were some that have high immuno score, high tumor-infiltrating lymphocytes that have high PD-L1 staining, and those patients seem to preferentially benefit from the addition of atezolizumab immunotherapy to placebo when combined with chemo and bevacizumab.

So we think we're now getting a little bit smarter, not only finding the right combination of drugs in the immunotherapy space, but also finding the right patients that can really preferentially benefit. So that's really exciting.

Dr. Turck:

Thanks, Dr. Weinberg. And, Dr. Kim, same question to you. What are your parting thoughts about refractory MCRC and its treatment?

Dr. Kim:

Sure, and I think I want to stress the importance of biomarker testing once again. I think that is very important to do at the time of diagnosis of advanced colorectal cancer, so you have a plan in terms of what kind of aberration and mutations patient may have. So you have a plan ahead to how to treat those patients.

Now in having said that, I think right now, in the future, we're still waiting to hear the results out from large phase 3 study in the refractory setting. For example, there is a trial combining PD-1 with LAG3 inhibitor phase 3 study that's, I believe, it has finished accrual. And there's an ongoing study with the immunotherapy and second-generation TKI. In this study, they're restricted to patients who are KRAS wild-type, interestingly enough. So I think those trials, hopefully, read-out, and hopefully, we'll find out if any subset of the patient were microsatellite stable or MMR proficient patients do benefit from immunotherapy. And I think they'll be the key in the future.

Dr. Turck:

It's a great way to end our discussion on this topic. And I want to thank my guests, Drs. Richard Kim and Benjamin Weinberg, for joining me to discuss the health burden and emerging therapies for patients with refractory metastatic colorectal cancer. Dr. Kim and Dr. Weinberg, it was great having you both on the program.

Dr. Kim:

Thank you.

Dr. Weinberg:

Thanks so much.

Announcer:

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