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<https://reachmd.com/programs/conversations-colorectal-cancer/the-role-of-targeted-therapy-in-metastatic-colorectal-cancer-patient-care/10272/>

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## The Role of Targeted Therapy in Metastatic Colorectal Cancer Patient Care

Announcer:

This is ReachMD, and you're listening to *Conversations on Colorectal Cancer*, sponsored by Lilly.

Dr. Johnson:

Thanks to advancements in targeted therapeutic options for metastatic colorectal cancer, or mCRC, survival rates are improving year after year, and as we continue to learn more about the cause of this cancer and develop new therapies, physicians now have the ability to create personalized therapy regimens. But how do they know which option is best for each individual patient?

This is *Conversations on Colorectal Cancer*, and I'm Dr. Shira Johnson. Here to talk about the role of targeted therapies in the mCRC care continuum is Dr. Edmond Bendaly, chairman and liaison of the Cancer Committee at Marion General Hospital in Marion, Indiana. Welcome, Dr. Bendaly.

Dr. Bendaly:

Hi, Dr. Johnson, good to be with you.

Dr. Johnson:

So, why don't we start with a focus on VEGF-targeted therapies and their role as newer therapeutic options are being tested? What can you tell us about this therapeutic approach for colorectal cancer?

Dr. Bendaly:

So, VEGF inhibitors are one of the earliest monoclonal antibodies and targeted therapies against the VEGF receptor, which, when activated, plays an important role in tumor angiogenesis. And so these VEGF-targeted therapies, by inhibiting VEGF receptors, can inhibit angiogenesis and lead to tumor death, and in metastatic colorectal cancer, they have historically played a very important role when combined with cytotoxic chemotherapeutic agents in the front line as well as subsequent lines of therapy. Their use has been close to around 15 years ago now, and they have shown improvement in outcomes across multiple lines of treatment in patients with metastatic colorectal cancer.

Dr. Johnson:

Is this option still prominent or central in current management approaches?

Dr. Bendaly:

Absolutely. There is a lot that we have learned over the last decade and a half in their clinical use, and we continue to learn quite a bit, especially with recent data published by the CRGB group and the sequencing with other targeted therapies across a wide variety of clinical pathological features, whether it is tumor sidedness or the EGFR mutation status of tumors. And to this day, these agents, specifically the monoclonal antibody bevacizumab, continue to play a very important role in the care continuum of our patients with metastatic colorectal cancer.

Dr. Johnson:

So, you mentioned EGFR therapies. What should our audience know about them?

Dr. Bendaly:

EGFR-targeted treatments are, for the most part, monoclonal antibodies that target the epidermal growth factor receptor, which is a transmembrane protein that plays an important role in the activation of the RAS, RAF and MAP kinase system, and that leads to cell growth and angiogenesis, as well as proliferation and mortality of the tumor cells and metastasis. And these monoclonal antibodies, they inhibit the interaction of these receptors with their ligand and therefore leading to inhibition of these different pathways.

What we have learned about them over the years is that they work in patients whose disease, whose tumors, have RAS wild-type status, and what we have learned is, in those patients whose tumors have mutations in RAS, whether it is KRAS or NRAS, those monoclonal antibodies do not work, and they are inhibiting the receptor which is proximal to the constitutively active RAS oncogene, so their use is very important in RAS wild-type tumors and actually detrimental in RAS-mutated tumors. And what we have learned over the last few years is that in the frontline setting, especially tumors on the right side of the

colon, even though they are RAS wild-type, efficacy of these agents is hindered compared to if the tumor was on the left side of the colon and had a RAS wild-type status.

Dr. Johnson:

Can you tell us a little about the side effect profiles for these drugs?

Dr. Bendaly:

So, some of the major side effects of EGFR monoclonal antibodies include infusion reactions, an acne-like rash that typically involves the face and the torso, as well as electrolyte abnormalities, mainly changes and disturbances in magnesium and potassium, in addition to some slightly increased risk of hematologic toxicity when combined with chemotherapeutic backbones, whether in the frontline or second-line treatment. And one thing to keep in mind is some of those electrolyte abnormalities can actually occur up to 6 weeks from drug interruption, so it's very important to make sure that we follow our patients, not only while on treatment but as well following therapy up to 6 to 8 weeks from drug interruption. They have a very low but serious chance of interstitial lung disease, so oncologists need to be on the lookout for any changes in respiratory status that could raise some red flags about this possible albeit rare pulmonary toxicity. VEGF inhibitors, on the other hand, have their own list of side effects, specifically proteinuria, hypertension, increased risk of wound dehiscence, and they interfere with angiogenesis and bowel perforation.

Dr. Johnson:

So, following up on the side effects that you mentioned, what is the role of the RAS mutation testing in identifying who would benefit from EGFR therapies?

Dr. Bendaly:

So, we have learned a lot about the RAS pathway and its central role, as I mentioned, in angiogenesis, cell survival and mortality invasion as well as proliferation and metastasis, and RAS is the first protein on the intracellular level across from the EGFR receptor that triggers this cascade, if you want, of activating RAS, which in turns activates MEK and self-activates the MAP kinase pathway. And because EGFR-targeted therapies are monoclonal antibodies, meaning they work on the outside of cells by interacting with the EGFR receptor, if the RAS protein itself is mutated and constitutively active inhibiting the EGFR, it's not going to have an effect on the downstream cascade, and therefore, testing all patients prior to initiation of EGFR-targeted therapy for not only the KRAS status but also the NRAS status is of paramount importance, as we have learned from a variety of studies that those patients whose tumors have RAS mutations, whether KRAS or NRAS, unfortunately, will not respond to those classes of medications.

Another nuance that we have learned recently is the sidedness of the cancer matters, and what that

means is, even though the RAS may be wild-type, those tumors located on the right side of the colon do not respond to EGFR inhibition as tumors that are located on the left side of the colon and are RAS wild-type, so extremely important to check the RAS mutation status as well as other potential tumor profiles such as the RAF and the microsatellite instability, preferably at diagnosis of metastatic colorectal cancer.

Dr. Johnson:

So, when patients have BRAF mutations, how do you factor that into their care decisions and the targeted therapies that are available to them with this mutation?

Dr. Bendaly:

The RAF oncogene is the downstream to the RAS oncogene, and we know that these 2 oncogenes are in a series of oncogenes in a cascade called the RAS/RAF/MEK and MAP kinase, which plays an important role in cell survival, metastasis, angiogenesis and proliferation. We know that monoclonal antibodies directed against EGFR, for them to be effective, an all RAS wild-type status of the tumor needs to be present. Otherwise, if there is any mutation in RAS, their efficacy will be hindered quite a bit. What we have also learned is, in patients whose tumors are all RAS wild-type, those tumors who have the RAS mutation, and that is around 5 to 10% of tumors, those may have decreased response to EGFR monoclonal antibody inhibition, especially in later lines of therapy. The small molecule tyrosine kinase inhibitor vemurafenib, when added to the chemotherapeutic agent irinotecan, and the EGFR inhibitor cetuximab or panitumumab, in those patients whose disease are all RAS wild-type and RAF mutated can overcome the lack of response in that particular setting.

Dr. Johnson:

For those just tuning in, you're listening to Conversations on Colorectal Cancer on ReachMD. I'm Dr. Shira Johnson, and I have the pleasure of speaking with Dr. Edmond Bendaly about targeted therapeutic options available for metastatic colorectal cancer.

Dr. Johnson:

So, earlier we talked about VEGF- and EGFR-targeted therapies, but now I'd like to switch gears a bit and talk about immunotherapies. What has the reaction been to this emerging therapeutic approach, and what kind of results have we been seeing?

Dr. Bendaly:

So, the era of immunotherapy used in metastatic colorectal cancer is relatively new. The target, however, or the molecular profile where these agents are effective we have known about for some time now, and what I mean by that is the microsatellite instability that sometimes characterizes some of the tumors. In tumors that exhibit a high level of microsatellite instability, which typically accounts between

5% and 9% of all metastatic colorectal cancer cells, that means that they are deficient in their ability to repair mismatches in their DNA, and that in itself leads to abnormal RNA, which leads to the translation of abnormal proteins, which leads to the development of epitopes on the surface of the cancer cell, and that in turn leads to the identification of those cells as foreign, and as a result, a mounting of an immune response against those cells.

Unfortunately, the normal immune checkpoint that our bodies have kicks in and inhibits this immune response against those cells through various immune checkpoints, one of which is the programmed death ligand immune checkpoint, and the monoclonal antibodies targeting this particular ligand wake up, if you want, the immune system again and allows it to recognize these cells as foreign and allows the immune system to mount again a response against those cells.

So, those tumors who exhibit a high level of microsatellite instability have been shown to be targets to immune therapy, specifically PD-L1 monoclonal antibodies such as the medications nivolumab and pembrolizumab, with very good response rates and improvement in survival, whether it is the overall survival or progression-free survival, and this has really pushed the continuum of treating our patients with metastatic colorectal cancer even further with really exciting outcomes.

Dr. Johnson:

So, before we wrap this conversation up, do you have any additional takeaway thoughts that you'd like to share with our audience today?

Dr. Bendaly:

We have learned over the last several years quite a bit about the important role of targeted therapies in the care continuum of our patients with metastatic colorectal cancer, and hopefully, we'll continue to learn and gain further insights to improve the outcomes for our patients with this disease.

Dr. Johnson:

That's a great comment for us to think on as we come to the end of today's program. And I'd like to thank Dr. Edmond Bendaly for sharing his insights on targeted therapies for metastatic colorectal cancer. Dr. Bendaly, it was great speaking with you.

Dr. Bendaly:

It was great speaking with you too.

Announcer:

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