Interview of Jessica Mitchell, RN, CNP, MPH

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TRACK 1 CASE DISCUSSION: A 38-YEAR-OLD SINGLE MOTHER OF MINOR CHILDREN WHO EXPERIENCES A SECOND MCRC PROGRESSION ON BEVACIZUMAB-BASED THERAPY RECEIVES AFLIBERCEPT/FOLFIRI

DR LOVE: I next met with Ms Jessica Mitchell for a nursing perspective on metastatic colorectal cancer, and to start the conversation she presented a patient from her practice: a 38-year-old single mother of 3 young children who presented initially with localized colon cancer and received adjuvant FOLFOX after surgery. Six months later she developed abdominal discomfort and was found to have biopsy-proven peritoneal and nodal recurrence, which responded to FOLFIRI/bevacizumab, but after 21 cycles there was disease progression on this regimen and the VEGF trap aflibercept was substituted for bev and FOLFIRI continued. This again resulted in a response, and the patient is currently continuing to receive this treatment. Ms Mitchell summarized the patient's current status.

MS MITCHELL: She's overall done remarkably well. And a remarkable thing to me is that once she started the FOLFIRI and aflibercept, she had about 9 cycles. And then just recently, she decided that she wanted to take a little break and have a vacation with her family, like sort of a holiday. So she was tolerating the drugs really very well.

I think one of the biggest struggles for her is that she's a single mother with 3 young children and no support of the father of these children. She has limited social support and, I would say, limited financial resources as well. So when she had this initial cancer and she said, "Okay. I just have to get through these 6 months, and then I'll be okay and I'll go back to, quote, normal. I can do this by myself." It was quite a devastating blow for her when it reoccurred, because all of a sudden she was confronted with: Okay. How am I going to deal with my children? She wanted to continue to see us, which was a 3-hour drive for her every 2 weeks. That's 6 hours. The finances of that, as well as the logistics of caring for her children during that time frame, and I would say the majority of time she came by herself. So I really felt like it was part of my responsibility in taking care of her to help provide some sort of psychosocial support, maybe even more so than my other patients, because I felt like she didn't have an outlet for that.

So we spent a lot of time discussing not only her side effects of chemo but also how she was dealing with her children and what was she going to do in the future and how were things going to potentially go. I felt like it was important for me to help her plan some sort of contingency plan for her children and their life. And I felt like that took us a long time to get to that level of trust where she was really opening up to me, but I felt like once we got there, it's been very beneficial for her. I actually think she's probably tolerated the drugs a little bit better, because I feel like part of our visits are more of like a psychosocial counseling session, which is, I think, an essential part of giving her appropriate care.

DR LOVE: Did she have questions about the issue of curability or not?

MS MITCHELL: Absolutely. She still asks me the same questions about, "Why can't we just go back in there? And why can't the surgeon just take out the spot?" She has multiple spots in the omentum. And she's done remarkably well, but we revisit that all the time, because it's a very hard diagnosis to really accept. And the finality of all of that and the future looming is — it's almost too overwhelming to even contemplate. So I think it's critical when taking care of patients. I always think, "I want to treat them the way that I would want to be treated." And I feel like part of that is being honest. I try to be kind and compassionate but also tell them the truth about what's happening and get them prepared for potentially the next step. I think that's really important, because to look back and have them think, "You kept that from me," or, "You didn't tell me that. And if I had known that, maybe I could have done this to prepare better or my children prepare better," or, "I wouldn't have had so much anxiety or anger going through this process." So we've always had a very open relationship.

DR LOVE: How old are her children?

MS MITCHELL: Now they're 6, 8 and 16.

DR LOVE: So has the subject come up, or are you aware of who's going to take care of these children if and when she dies?

MS MITCHELL: Absolutely. Actually, we had a really hard conversation about 6 months ago. And I said, "You've got to think about them, and we really – you need to think about making a will and what's going to happen to them, because the worst possible thing is to leave them with no plan." And being a mother myself, I just think you have to think about these little people that are your responsibility. So she actually — that was really difficult. I think she was actually kind of angry at me for suggesting that, but she did make a will. Her sister actually moved from a different city back to the city that they live in. And when her death comes, her sister is going to take the primary responsibility for those children. Her parents are going to help, but coming to that resolution was enormous. Because there is no other half. There is no father to provide support for these young children.

DR LOVE: What kind of work is she doing or has she done?

MS MITCHELL: Unfortunately, she lost her job. She was working at a cell phone store. And she was gone so much coming back and forth from trips to see us, as well as taking a couple of days after chemotherapy to recover, that she was let go. They gave her other reasons why she was let go, but she was actually a top producer and salesperson before her diagnosis. And then once this all started, she lost it. So we went through the process of getting her federal aid and food stamps and accessing some resources like that for her as well.

TRACK 2 USE OF ALTERNATIVE AND COMPLEMENTARY THERAPIES FOR PATIENTS WITH MCRC

DR LOVE: What level of interest does she have in understanding about the treatment she's getting, understanding her disease? Has she tried to read up on that or not so much?

MS MITCHELL: Constantly. She's on blogs all the time about metastatic colon cancer. And she's always coming to me about the latest, greatest new herbal technology. She actually was asking me about aflibercept like right after it was approved, when none of my other patients really had any idea. She's always trying to figure out what's the next thing I can get access to. She doesn't want to run out of options.

DR LOVE: You mentioned herbal. Did she have any interest in complementary or alternative treatments?

MS MITCHELL: She does, and she did. She went to our Complementary Medicine Department and got some really good suggestions, but since then she does reflexology on her feet weekly. She does acupuncture. And she gets a reduced cost for these resources. And I know she takes a lot of supplements. I don't actually think she tells me everything she's taking, because I think some of it is good and some of it I just can't give her any advice on. So I've always told her, "There's a high probability that they may interact with some of your chemotherapy drugs, and you don't want to undo what you're trying to do," but I know that she uses a lot of extra.

TRACK 3 COMMUNICATING EXPECTED RISKS AND SIDE EFFECTS OF CHEMOTHERAPY TO PATIENTS

DR LOVE: So the initial treatment she received for her metastatic disease is very, very common, particularly in patients who had prior adjuvant FOLFOX, which she had. Incidentally, how did she do with that? Did she have any neuropathy?

MS MITCHELL: She did have neuropathy. It wasn't severe. And she actually did, I think, quite well, though neuropathy is — after about I'd say about 4 months, it was pretty much resolved.

DR LOVE: So what actually happened when she got the FOLFIRI/bevacizumab? First of all, what happened in terms of her hair? And how did that compare to her hair on FOLFOX?

MS MITCHELL: Yes. That was a tough one for her, because on FOLFOX she didn't lose any hair. And on FOLFIRI, I try to remind patients that every chemotherapy agent is different and carries its own side-effect profile. So lots of times women, in particular, they'll see patients that are breast cancer patients, and they'll see them bald. And that's not the way irinotecan typically works. That's usually from a different drug like paclitaxel. Irinotecan is a slow hair thinning and eventual loss the more that you get. Sometimes I think that's better, because you can kind of prepare for it, and sometimes it's worse, because it's this long, protracted process of losing your hair. And people say, "I just want it gone already. Let's just do it."

But for this patient, it was a slow hair thinning over time and, eventually, we did do a prosthetic — like a wig, which was helpful. And she wore hats, but for her it was helpful that it wasn't just all of a sudden. It was like a slow hair thinning. And I think part of that is because it wasn't as shocking for

her children to see their mom all of a sudden lose their hair, I think, would have been harder for her children than, "Oh, I'm slowly losing it, and now I'm used to it. I know what to anticipate, and mom's going to use a wig now."

TRACK 4 COUNSELING PATIENTS WITH METASTATIC DISEASE ABOUT DISCUSSING CANCER AND ITS TREATMENT WITH THEIR CHILDREN

DR LOVE: Have you met her children?

MS MITCHELL: I have.

DR LOVE: She brings them to clinic?

MS MITCHELL: She does. We talk about them quite a bit, so she wanted me to meet them. And I think that she must talk about me, as well, at home. So yes. And I actually think that's a really beneficial thing, because it takes the mystery and the scariness away from what she's going through. And you can see, "Oh, this is a place where mom's getting healed. And this medicine is helping mom. It's not hurting her," and, "Look at how nice everybody is here," and that, for a little person, I think is really helpful.

DR LOVE: This, of course, applies in many different tumor types, but I am curious what you think is appropriate to discuss or advise your patients to discuss with minor children in a terrible situation like this based on age.

And looking at her children, how did you advise her, if she asked, or how would you have advised her in terms of how to answer their questions?

MS MITCHELL: That's an excellent question. I think that's a really tough one. I've had unfortunately many patients that have had young children. And I think you have to meet people where they're at. And to tell a mother or father, "You need to tell your child that this many months, mom's not going to be here," and "This is what's going to happen," particularly when you're 6 and 7, that's really hard. I mean, to understand the concept of death, even for adults, is very difficult. So I tell people it's good to be slow and gentle, because I think surprising children with all of a sudden mom's gone and what happened isn't fair either, because I think children are smarter than we give them credit for as well. And they can see what's going on with mom physically. So for these children, she would say, "Mom's sick, and this is the medicine that's going to help mom get better," and, "We don't know how much time mom has, but every day that we have together is a gift and we're going to spend it together," and, "Mom loves you and, no matter what happens, mom's going to make sure that you're going to be okay," because I think that sense of security for children — like, if mom's gone, particularly if dad's not there, "What's going to happen to me?" To make as much as you can that gives them reassurance that no matter what, somebody loves them and will take care of them is critical.

DR LOVE: So do you think that, for example, the 6-year-old understands or is aware that her mom is going to die?

MS MITCHELL: No. I don't think that she really conceptualizes that. But it's interesting, because on some levels she's very — since this has been going on over the last few years, she's becoming increasingly more attached to her mother. She gets really nervous when she can't see her mother or she doesn't know exactly where her mother is. So I think on some level, she does understand that she's going to lose her mom.

The older ones, especially her 8-year-old, I do think understands what's happening and has moments where he's really, really scared. And he unfortunately has not been to a counselor. I'm not really sure why they haven't done that, but I have had other patients who have. And I think that's very helpful, too, because children have emotions and feelings, and sometimes they don't know how to articulate them. So finding ways for them to get them out through play or stories is critical.

TRACK 5 RESPONSE TO AND TOLERABILITY OF FOLFIRI/BEVACIZUMAB IN MCRC

DR LOVE: So let's focus more now on her specific treatments. When the FOLFIRI and bevacizumab was started, how did she do in terms of side effects and other issues, and how did she do in terms of the tumor?

MS MITCHELL: She had a remarkable response. And actually, she tolerated it quite well. She did have the hair loss. She did have a little bit of diarrhea, no real significant impact on her red/white blood count. She had no hypertension, which is amazing. And she really went along with her life quite normally. I would say she had quite a bit more fatigue, particularly in the later cycles. And I think that was the burden of having so much treatment for so long, so I think it's probably partially mentally, partially physically, because she received a total of 23 cycles, which is pretty phenomenal. And she was a person that never really wanted to extend the duration between her treatments. At this point of her treatment, I mean. And didn't want to take, quote, chemotherapy holidays. She wanted to stay on this every 2-week

cycle pretty regimentally because she just felt like, "I've got to do everything I can and this is what you said to do, and this is what I'm going to do." So I think at the end it was pretty tough.

DR LOVE: So that was for about how long was she on the FOLFIRI/bev?

MS MITCHELL: So that was about a year and a half, maybe a little bit over that.

TRACK 6 SUPPORT SYSTEM FOR PATIENTS COPING WITH MCRC AND ITS TREATMENT

DR LOVE: And during that time, during that year and a half, what was her personal life like? What was going on?

MS MITCHELL: I mean, there's a lot of struggles. In that year and a half, she lost her job, which was really difficult. In that year and a half, I think she came to the real understanding of her disease and the chronicity of it and how she was going to have to deal with this for the rest of her life. I think there's quite a bit of stress with her children. Remember, she also has a teenager, and dealing with a teenager, going through his own independent teenager-related issues, and then her own issues on her own, financially it was tough on her. So I think that was a really hard year and a half for many reasons.

And I think that she's somebody that didn't have a lot of anger. Sometimes patients get very angry about "Why me," and "This isn't fair," and "I'm a single mother," and she didn't have that, interestingly. And I don't know why, because, if anybody, she really probably should have. I mean, with all of the things that she was confronted with, but she just felt like it happened to me, and now I have to deal with it. It was all these other things about like having to do with her children and the finances and that sort of thing. But I don't think she's ever looked back and said, "This isn't right. It shouldn't have happened to me." I think she thinks it could have happened to me or my neighbor.

DR LOVE: Who is her adult support? Did anyone ever come with her to the clinics?

MS MITCHELL: Her parents have come a few times. And her sister has come a few times. But I think she's had one other friend come maybe once or twice during the whole time of taking care of her. But most of the time she comes by herself. I think probably she has other people come, and they wait in the waiting room, and I just don't know about it, because like I said, a lot of our time is spent in really dealing with a lot of the psychosocial issues that she's having. And I don't think that she necessarily wants everyone to be aware of everything that she's thinking and feeling, which I can respect that.

TRACK 7 MANAGEMENT OF BEVACIZUMAB-ASSOCIATED HYPERTENSION

DR LOVE: So you mentioned the fact that she did not have hypertension, which is not uncommonly seen with bevacizumab. I'm just kind of curious when you do see hypertension with bevacizumab, how easy or difficult is it to manage?

MS MITCHELL: It depends. I think it's a little bit more difficult when someone has preexisting hypertension or preexisting cardiac problems. It's more difficult because you can wind up on 3 or sometimes 4 different antihypertensives. And it's been my experience that the calcium channel blockers, particularly amlodipine, seem to work most effectively. I know that the recommendation is you sort of follow the standard antihypertensive regimen or standard of care, but I really feel like amlodipine is the best. So if someone's on, let's say, hydrochlorothiazide or valsartan or something like that, I'll usually add to that amlodipine. And I can usually obtain a response.

I have had few and far between patients that I've had to hold their bevacizumab for hypertension.

TRACK 8 CONTINUATION OF ANTI-ANGIOGENIC THERAPY AFTER DISEASE PROGRESSION ON FIRST-LINE THERAPY FOR MCRC

DR LOVE: You mentioned that initially she had some sort of abdominal discomfort or some kind of symptoms in the abdomen. Did they change at all after she got the FOLFIRI/bev?

MS MITCHELL: Yes. They did. They improved. And that's how she felt like it was working. She has this pelvic fullness. It's just, like, a difficult-to-describe feeling that she has. And when that goes away, she feels like, "Oh, things are working," and she's usually right. She doesn't really have pelvic ascites, so I don't really know what she's feeling, but you definitely have improvement when her symptoms improve like that.

DR LOVE: And you said there was a nodule that you could feel?

MS MITCHELL: Right. There was a really small — when she was initially diagnosed, when the cancer returned, on the left upper quadrant. It was like about the size of maybe a little bit bigger than a dime, that you could feel. It was like a little palpable nodule. That's what we biopsied. And that has shrunk. And then it sort of stayed the same size. So…

DR LOVE: So after a year and a half of treatment, which sounds like was successful to some extent, she then, like many patients, if almost all, did show some disease progression at that point, I guess, on her imaging studies. Now, at that point, was she still feeling well?

MS MITCHELL: She was.

DR LOVE: And was this a big change in what was seen or just a small change?

MS MITCHELL: Just a small change.

DR LOVE: So she then was considered, though, clinically progressing, correct?

MS MITCHELL: Correct.

DR LOVE: And she then, I guess, really the team then was faced with really one of the most controversial decisions being discussed nowadays in colorectal cancer, which is exactly this situation, the patient who's had a very good response to first-line therapy with chemotherapy and bevacizumab, certainly the most common approach to metastatic disease nowadays. She responds, but then she has slow progression. And so a couple of the strategies that have been thought about in this situation, one is to switch to some other type of anti-angiogenic. And there is a newly approved agent, aflibercept, that's available. But also there's another strategy that's often considered, which is to keep the bevacizumab going and change the chemotherapy, which seems to have similar benefit to aflibercept.

When you faced this situation, were these the 2 things you were kind of thinking?

MS MITCHELL: Absolutely. And a lot of it had to do with the duration of what she was treated with the FOLFIRI and bevacizumab, because she had done so well for so long. We thought, "Maybe there's still some activity out of these drugs," and you know when you're treating somebody with metastatic disease you want to utilize these drugs as long as possible. And when it's clear, either by symptoms or radiological progression, that there's no more utility in these drugs, then you want to switch. So although we had options of, let's say, aflibercept or — she's KRAS mutant, so she would not be eligible for cetuximab.

DR LOVE: I guess we should point out, though, that, what, about half of the patients have a KRAS mutation in their tumor. And we know those patients don't respond to EGFR antibodies like cetuximab.

MS MITCHELL: Exactly. So that somewhat limited our options as well. And being the savvy patient that she is, she knew about aflibercept. And she also had some ideas about what her next treatment should be. And she really wanted to try the combination of FOLFIRI and aflibercept, which after much discussion, we felt like that was a reasonable thing to try. And actually, it's been helpful for her.

DR LOVE: So how long has she been on that treatment?

MS MITCHELL: Oh, now it's probably about 5 months.

TRACK 9 COUNSELING PATIENTS ABOUT THE POTENTIAL SIDE EFFECTS OF AFLIBERCEPT

DR LOVE: And what did you discuss with her when this treatment was beginning in terms of potential side effects and toxicity, and what did she actually experience?

MS MITCHELL: With aflibercept there's the same potential as bevacizumab for hypertension and proteinuria. So she knew that risk factor. I did tell her specifically with aflibercept, though, there's a higher potential for neutropenia, which she did experience. And we hadn't seen that previously in her other regimens.

She also had a little bit more diarrhea and she had a macular rash that was raised, red, mostly on her forehead and cheeks. Not symptomatic, not pruritic, not bothersome, nothing like an EGFR-induced rash, but noticeable. And those risks she was willing to accept for a benefit.

DR LOVE: I guess we're still trying to tease out exactly the potential side effects and toxicity with aflibercept, but what you talked about, maybe having a little more toxicity than seen, for example, with bevacizumab. And I've heard people talk about the fact that it seems like there's maybe more chemo toxicity in these patients. And I've heard people say that maybe the normal tissues don't rebound, the marrow, et cetera, maybe doesn't rebound as well, which is maybe why they get more neutropenia. What actually happened? Did she have an infection with the neutropenia?

MS MITCHELL: No, but she went from a normal count, about 4,000, to about 900. She did that a few times. We actually did end up reducing the dose of the aflibercept. She did better, but actually I just saw her about 2 weeks ago, and she called complaining of fever, rigors, chills and she was very neutropenic. Her neutrophil count was only 500. And that was at her nadir, about 7 days after her chemotherapy. So I suspect we're going to give her an extra week off. But when I see her again, I think we'll have to further dose reduce the aflibercept. It's interesting. It does seem to somehow potentiate the effects of

the irinotecan a little bit, because you definitely have more of the neutropenia and the diarrhea, but I don't think that's ever been studied.

TRACK 10 CONSIDERATION OF REGORAFENIB AS LATER-LINE THERAPY FOR MCRC

DR LOVE: So unfortunately, again, you might expect that at some point in the future, this strategy might not continue to work and she might again have disease progression. One option at that point might be to go back to bevacizumab, maybe change the chemotherapy. I mean, theoretically, she could get FOLFOX or something like that again. But beyond that, what are some of the options that you think might lay in her future?

MS MITCHELL: Actually, we've had a lot of discussions. She always wants to know what's the next thing. And I think you bring up a good point, revisiting some of these drugs. In particular, the FOLFOX and FOLFOX plus the bevacizumab would be potentially beneficial. We've also discussed the possibility of using one of the newer agents, regorafenib, which I think would be also an option for her. And beyond that, we'd have to kind of think a little bit more in the clinical trial realm, probably, for treatment options for her.

DR LOVE: So that does really lead into the question of regorafenib, because it really is in patients like her and most people with metastatic disease, when you kind of get beyond the basic chemotherapy and biologic strategies, anti-angiogenesis, and if they don't have a KRAS-mutant tumor, one of the EGFR antibodies. And that's kind of where this new more recently approved agent, an oral TKI, tyrosine kinase inhibitor, regorafenib comes into play.

TRACK 11 CASE DISCUSSION: A 53-YEAR-OLD PATIENT WITH KRAS WILD-TYPE MCRC WHOSE DISEASE PROGRESSES THROUGH MULTIPLE LINES OF THERAPY RECEIVES REGORAFENIB

So with regard to regorafenib, I know you had another patient, a gentleman with metastatic disease that received this drug. Can you talk a little bit about his situation at the time at which he started the regorafenib?

MS MITCHELL: So this is a 53-year-old male that I had taken care of with metastatic colon cancer primarily to the liver. At the onset of his diagnosis, we checked his KRAS status to see if we could give him the drug cetuximab in the future, and he was KRAS wild type. So we knew that was going to be an option, which was very beneficial. But we decided — he had no concerns regarding the possibility of perforation, because his primary colon cancer was going to be left in place due to the extensive disease in his liver. He was never going to become a resectable candidate. So we started him on FOLFOX and bevacizumab. He did quite well on that, really had minimal side effects, but over about the 9 months that he was on that drug combination, he did develop neuropathy that really got to him at the end of the treatment, to the point where he was contemplating, "I don't know if I can take much more of this."

Unfortunately, around that same time, we did a CAT scan and he had evidence of progressive disease in the liver. So after that we put him on FOLFIRI. And we did keep the bevacizumab going.

DR LOVE: So that's the strategy we just talked about related to your other patient, of keeping the bevacizumab going and switching the chemotherapy.

MS MITCHELL: Absolutely. And it actually worked really well for him as well. Again, he tolerated this for quite a bit of time. I think on this regimen, he was probably on it about 7 months and did well. He did have some of the side effects from irinotecan, in particular diarrhea, which was actually kind of a struggle for him. But we were able to work through that with a very stringent and diligently applied bowel regimen on his part. And then he had evidence again of progression.

So we decided that we would give him irinotecan and cetuximab. And he did extraordinarily well on that. He had a florid EGFR rash, which we tried to attenuate a bit with the STEP protocol, skin protocol, which worked really well for him. And then after that, when he had progressive disease again, that was a little shorter interval. That was about a 4-month interval. We decided, looking at our options, that we would try regorafenib. We wanted to try a novel approach instead of, for instance, aflibercept and FOLFIRI.

So he was given regorafenib. But from our prior experience with other patients on this drug, we decided instead of starting him at the full 160-mg dose, we would instead start him at a 50%, or 80-mg dose, and slowly escalate him based on his side effects.

That strategy worked really well for him. We were somewhat concerned about how he was going to tolerate the regorafenib, because due to the liver-dominant disease he had, at baseline, abnormal liver function tests. Not strikingly so, but his alkaline phosphatase was about 220 and his AST was about

60. So what we decided to do was weekly blood draws, monitoring his liver function tests, and also daily blood pressure checks for high blood pressure. And we started a very stringent skin care regimen with him to try to prevent the hand-foot syndrome.

TRACK 12 PREVENTION AND MANAGEMENT OF REGORAFENIB-RELATED HAND-FOOT SYNDROME

DR LOVE: When you first started the regorafenib on him, what were some of the things that you went through with him from a patient education perspective in terms of what to expect and what to report to you?

MS MITCHELL: Absolutely. So I think the regorafenib can be a reasonably well-tolerated drug, if the patient is well aware of helping to prevent some of the significant side effects. From my experience, I see the hand-foot skin reaction to be quite different than previously experienced on other chemotherapy agents such as capecitabine. This hand-foot reaction syndrome can be severe. And it's really quite rapid at onset. It really is, instead of a redness and swelling and uncomfortableness you have in your hands and feet, this is really like a blistering. And the blistering is on the places where patients really put the most amount of pressure, so on their heels, on their hands on the palmar surfaces. And so we always tell patients, "It's very important that you have you or your spouse or your friend check your hands and feet every day. You put a very rich emollient cream on your hands and feet. Try to sleep with gloves and socks to keep the skin moisturized. If there's calluses, you need to try to remove them as conscientiously as possible, and really monitor that."

And, "If you develop this hand-foot skin reaction, you need to stop the drug and make sure we're aware of it, and then we can appropriately adjust the drug dosage."

The other thing is high blood pressure. So we need to make sure that the blood pressure is taken every day and a record is kept, so that if we need to we can start appropriate anti-high blood pressure medications early and not have any significant elevations in the blood pressure. And also, the liver function tests, I think, are critical. I always have patients for the first 2 cycles — which is the first 2 months — check their blood work every week and fax it to me. And then I always call them, as I did with this patient, and we say, "Okay. Everything's going okay. Your liver tests look fine. We can continue on," or, "We need to take a break and stop. Liver function is getting a little bit elevated, and then we'll readjust the dose." I think close monitoring such as that is critical for success of this drug.

DR LOVE: And I guess we should mention that this is an oral tyrosine kinase inhibitor. There are a lot of TKIs in oncology nowadays. And one that's very similar to this one, regorafenib, chemically — I think there's like one molecule difference or fluorine difference — is the drug sorafenib, which is used in renal cell cancer and hepatocellular cancer. And there, the hand-foot syndrome is also a problem that comes into play. Are these two similar from a toxicity point of view?

MS MITCHELL: Yes. However, also, with sorafenib, we tend to start at a 50% dose reduction and slowly escalate the dose. I do think, from what I've seen with regorafenib, that the onset of the dysfunction in the liver tests seems to be much more rapid than with sorafenib. And the severity of the hand-foot syndrome also seems to occur more rapidly and with more intensity than I've seen with sorafenib.

TRACK 13 CLINICAL EXPERIENCE WITH AND TOLERABILITY OF REGORAFENIB FOR MCRC

DR LOVE: So what happened to this man as he was taking the regorafenib?

MS MITCHELL: So, he started at 80 mg. He did really well. After the first cycle, or month, the second cycle we started him at 120 mg. And he tolerated that well. We did try to escalate the dose at cycle 3. He could not tolerate that. The liver tests started to get too abnormal, so we kept him at 120 mg. And he's been on that now for the last few weeks, and he's doing well. He really has been quite diligent about maintaining his hands and feet. He did have some blistering, particularly on his soles, but we did have a slight interruption. And that really happened at the first cycle. We stopped the drug for a week, let him recover, and then restarted. And he did really well. He's been very proactive, however, and very involved in his care, which I think is essential. This is a drug that you can't take lightly and you really have to have the patients buy in for managing their side effects on really a daily basis to have a reasonable tolerance level.

DR LOVE: And I guess when the drug was approved, the idea was it was a later-line treatment, which more and more people with metastatic colorectal cancer are receiving. And when you get beyond the usual therapies in terms of FOLFOX, FOLFIRI/bevacizumab, the EGFR antibodies, if they're eligible to receive them, and yet when they studied this drug, regorafenib, in that late-line situation, they actually saw a survival benefit. And the next thing we know it was available. Any other comments about your experiences with this drug in terms of tolerability?

MS MITCHELL: Again, I think the biggest key here is adequate patient education. I think — it's a new drug on the market. And I think the oncological community is still becoming familiar with the drug and getting experience is key. But I think if we kind of don't go by the package inserts at the onset, with the knowledge that if we start low and go slow, we ensure better tolerance with the hope that we can dose escalate after cycle number 2, because that's really where you get the most amount of symptoms. I think that that takes some of the mystique away from that drug. And I think if we can do that on a more routine basis, we're probably going to have greater patient tolerability and ultimate hopeful success with the drug, because I think it's a good drug. It's just you have to inform patients that these are the known side effects. "This is your responsibility to make sure that you check for these things. And if there's any questions, you call me." There's a lot of resources out there to help patients, also, with educating on this process.

TRACK 14 IMPORTANCE OF FAMILY SUPPORT AND RELIGION IN COPING WITH A TERMINAL ILLNESS

DR LOVE: I'd like to get more of a personal look at him. What's his type of work that he is doing or has done in the past? And what's his family situation?

MS MITCHELL: He is a retired mailman. And he has a wife who is very helpful and loving and very involved in his care and his life. They have an excellent relationship. They've been married, I think, 35 years. They have 2 children. He has 4 grandchildren. They all live in a small farming community in the northern part of Iowa. He's somebody who really had no other health problems besides this cancer when it was diagnosed, so coming to terms with the fact that he is on all these medications and has a terminal illness has been difficult, but he's also a very religious person, and I know he draws on that to a large extent to help him cope with his situation.

DR LOVE: Is that a topic, his religion, that comes up in your conversations with him?

MS MITCHELL: We don't talk directly about his religion, but he will often tell me, "I know I'm going to a better place, and I know that I'm being cared for and that this is my path in life. And God is with me no matter what happens," and I think he finds a lot of peace and strength in that, because I think for him, dying is — he's going to a beautiful place that he's always learned about throughout his lifetime and that he finds will be better than the life he's living now. That being said, he does love his wife and family very much, and I know he mourns for that loss. But his wife is also very religious and she always says, "I'm going to meet you there." So they have a remarkable relationship and strength. And I think it's always hard for — I always think of the spouse to deal with this, because they have their own grief issues and loss. And it's very difficult to know what to, quote, do to help your spouse, because there's not much you can do. So I think for this particular family, they're very lucky, because the wife doesn't shoulder the whole responsibility. She has her children and her grandchildren and they all are part of coming to the visits and trying to help with their mother and support her, because I think that that's a very difficult thing.

And I always, when I meet people for the first time, I always think, "I'm taking care of the patient, but I'm also taking care of the family," because I know when this person is in the last dying stages of their life, I'm going to be focused mostly on the spouse and the family. And I have a lot of patients that will come and see me and write me notes and have ongoing relationships after the patient has passed. So I think it's not just taking care of that person. It's taking care of or trying to take care of that whole unit.

TRACK 15 MANAGING DERMATOLOGIC TOXICITY IN PATIENTS RECEIVING CETUXIMAB THERAPY

DR LOVE: So from a patient education perspective, I just wanted to circle back and talk about another issue that actually was part of this man's history, so maybe we can reflect on that, which is EGFR antibodies. And he received cetuximab. And you mentioned a little bit about the fact that he had a problem with the skin, that certainly a lot of patients have, and you used the so-called STEP protocol. So can you talk a little bit about your own experience with EGFR antibody dermatologic toxicity and different ways to prevent and treat it?

MS MITCHELL: Sure. It's interesting. This has really evolved since EGF antibody drugs were first approved. When we first gave the drug, cetuximab, we would tell patients — this is before we knew about KRAS — we would say, "Oh, we want to see the rash. The bigger, the badder the rash, hopefully then that means the more you're responding to the drug." So patients would really suffer with these horrific rashes that would bleed and cause a lot of pain and swelling and redness and can be quite disfiguring. But since then, we've evolved, thankfully, and now we have this wonderful skin protocol that's really used in more of a prophylactic sense. And I have seen remarkably different outcomes when patients utilize this protocol. So I am a very big proponent of it.

And really what it is, is you put 1% hydrocortisone cream on the places that the rash most often occurs, which is really on your face, your chest, your back, and your arms. And then you use doxycycline, 100 mg twice a day, religious use of sunscreen and a topical lotion that is free of any fragrance and would be hypoallergenic. That regimen happens twice a day. So the application of all those creams and the antibiotic every day as long as you're on the EGFR inhibiting drug.

And really, it doesn't prevent the rash from happening, but it significantly decreases the rash and the underlying disfiguring component of it, as well as the discomfort to the patient. So I think it's an excellent strategy that I hope everybody really utilizes.

DR LOVE: I've heard people talk about the potential social stigmatization of this type of rash and patients who have uncontrolled problems with the rash feeling socially isolated. Is that something you've ever observed yourself?

MS MITCHELL: Absolutely. And in particular, that was really with patients that inconsistently use this STEP protocol or before, when we didn't use it at all. But I've had patients — I always tell people, "The rash is not like a, quote, rash. It's like acne that teenagers get." Florid, macular/papular lesions on your face, exactly where you don't want it to be. So you can imagine the alteration in your self-perception is significant. In particular for women, but I would say the same for men. And patients wake up and they look in the mirror and they think, "Psychologically I'm dealing with this cancer, and it's so difficult to come to terms with, and then I look in the mirror and I just — I don't even look like myself. I have no hair, and then I have — my skin is all erupted."

And it's awful. And some patients, their face bleeds and they'll wake up and there'll be blood all over their pillow. And that, in and of itself, is just a terrible thing for people to have to go through.

DR LOVE: Any other side effects or problems that you see with EGFR antibodies?

MS MITCHELL: Really, the rash. I mean, there is a possibility of an allergic reaction. Fortunately in our community it's very uncommon, but our chemotherapy nurses are incredibly vigilant about watching people, particularly when they're first getting the drug, about allergic reaction. We try to premedicate for that. But fortunately, if it does happen, people can use an alternative EGF-inhibiting drug such as panitumumab, which would provide similar benefit with a significantly diminished chance for allergic reaction. But the reaction can be significant, severe.