Dr. Shepard - DTRF 2022 Patient Meeting Webinar #3

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Jeanne Whiting: Our second presenter will be on medical decision making for the systemic treatment of FAP-associated desmoid tumors presented by Dr. Dale Shepard MD, PhD, FACP, and Director, Phase one and sarcoma programs at Cleveland Clinic. Dr. Shepard, thank you for joining us.

Dr. Dale Shepard: Well, thank you very much for the introduction to present. Can you see my screen?

Jeanne Whiting: Yes, you're good to go

Dr. Dale Shepard: And you can hear me okay?

Jeanne Whiting: Yes.

Dr. Dale Shepard: All right, very good. So, as you mentioned Dale Shepard, I'm a medical oncologist and I oversee our sarcoma program. And I'm at Cleveland Clinic and with the just mentioned Weiss Center.

We have a large population of patients with FAP. And so, I frequently see patients coming in with desmoid tumors and you know, oftentimes they've come in and their local oncologists may not be particularly familiar with them, but they seem to be much more familiar to us because we see a lot of them.

And so, I guess the I'm gonna just talk a little bit about, really focus on kind of the treatments available, the medical treatments, but really kind of a thought

process now, how we think about the most appropriate therapies that we're gonna give from a medical side. My colleague's gonna talk more on the surgical side here in a bit, but from a medical treatment standpoint the very first thing, desmoid tumors, much like any type of tumor.

And I guess just to to reiterate a little bit with what Dr. Hurley had suggested, patients come in confused oftentimes because they have this thing called the desmoid tumor, and maybe that hasn't been described well to them. And you know, tumors in general tend to be scary to patients, but this isn't a cancer per se.

It's a benign, it's an aggressive, benign tumor. And I kind of described it as it's it's like a cancer because it grows in an uncontrolled way. It's not like a cancer because it doesn't grow into adjacent structures. So if it's up against another organ, it doesn't grow into that organ. And they also don't metastasize, they don't spread other parts of the body.

So, you know, when I first meet patients I like to oftentimes, if they're not, if they haven't really had a good overview of what desmoid tumors are, at least give them a little bit of a peace of mind because that's one of the biggest concerns sometimes because they have come to a cancer center to see me and they're like, Well, no one told me this is a cancer.

So reframing is is oftentimes important. So first thing when we think about is, you know, what are the goals of our care? What are we trying to accomplish? Are we trying to shrink a tumor? Are we trying to really not necessarily shrink the tumor? Are we just trying to keep it from growing more? Or do we have symptoms?

Is the desmoid tumor there but asymptomatic? and, you know, do we have a large desmoid that's pushing on something that it shouldn't. You know, desmoid tumors can cause trouble when they get big and start pressing on vital structures. And so do we need to do something that we can not only shrink the tumor but doing more quickly?

So those are some of the things we have to think about from the very onset is what's our goal? Cuz that's gonna determine what we're gonna do from a medical side. And this is something that, this is a a figure from the Desmoid Tumor Working Group that that really I think in a lot of ways that at the very top sort of defines something very important with desmoid tumors.

And again, Dr. Hurley was just talking about resilience. And resilience is important in this particular disease. This is a disease that most often patients are gonna have to have under control for very long periods of time. Once a diagnosis has been made a very common approach now is really just to get a sense of what that disease is doing from a biology standpoint.

Is it growing? Does it need an immediate therapy? So there's more of an emphasis now on what we're calling active surveillance. If we see a patient, they have a desmoid tumor, and again, we're talking about things that are not really large and not really symptomatic and not things that we definitely need to move on.

But oftentimes, getting a really short interval scan a month, a two, two months, three month scan, get an idea of growth. When you first see that, that, that imaging that shows a desmoid, you don't know how long it's been there. And in many cases the biology of desmoid tumors are that they can stay stable for long periods of time, untreated they can get smaller on their own without any treatment whatsoever.

So we'll talk about some trial data in a little bit. We'll help highlight that. But active surveillance is a really important consideration when we first diagnose a desmoid tumor. The sort of knee-jerk reaction sometimes to patients is, I have a tumor, I want it out. We'll let the surgical our surgical colleague talk about the role of surgery.

But more and more because of concerns for recurrence and really less aggressive surgical management may be the right call. If a tumor is shown to be progressing, you know, a lot of the next steps depends on where that tumor's located. Is it in the abdominal wall? Is it inside the abdomen, in the extremities is it in a head and neck region?

And we're talking specifically about FAP-associated desmoid tumors here today. FAP-associated desmoid tumors tend to be intraabdominal retroperitoneal. Patients I see with sporadic or spontaneous desmoid tumors much more likely to be in the abdominal wall or in an extremity in arm, a leg in under the arm, but far more likely the FAP-associated to be inside the abdomen.

And those are the ones really we start thinking about medical therapy. So what kind of medical therapies are we considering? We think about traditional approaches. The traditional things that have been looked at in the past would include non-steriodal anti-inflammatories hormonal therapies, targeted therapies, and of those, there's two drugs, pazopanib or sorafenib.

And then there's chemotherapy and there's a couple of different chemotherapy regimens that have been used in the past. And we'll talk about each of these. If we talk about non-steroidals, then there's a fair amount of work with non-steroid anti-inflammatories that took place over the years at Cleveland Clinic.

One of the, one of the non-steroid anti-inflammatories that is frequently used in patients that were going to be using non-steriodal anti-inflammatories is a drug called sulindac. The, well, one, if you look at actually some of the guidelines, if you look at the National Comprehensive Cancer Network guidelines, which is a, it's a group of a number of institutions where there are people who get together that treat sarcomas, desmoid tumors, and kind of come up with guidelines in terms of recommendations based on data.

They list sulindac as a drug that could be used in some situations. And part of the reason it's not sometimes given a higher level of recommendation is there haven't been randomized trials. There haven't been trials where that really have shown good benefit. There haven't been good trials where you give sulindac to one group and you take another group and you give another drug or placebo and see what happens.

This is actually data that came from going back and doing a chart review and looking at a number of patients, identifying patients that had desmoid tumors, looking to see what drugs patients had received, and then seeing if there was a benefit. And then this particular case, patients that had gotten sulindac actually did pretty well.

There was one patient that had a complete remission. Complete remission means that on follow up scans, there's no evidence of disease whatsoever. Seven patients had a partial remission. That means that it was still, it was still present on the scan, but you, it was it, there was a significant decrease in size, and four patients had four patients had disease.

That was what was be considered stable. Two patients had progression. So if you look at again, not in a randomized sort of way, but certainly there were patients that had a response. And when we think about the complications of desmoid tumors, one of those complications oftentimes is pain.

And so it sort of serves the purpose of being able to control pain and being able to at least stabilize and perhaps make the tumors smaller. So, you know, oftentimes, particularly in patients with FAP-associated because of the limitations and the therapies that are currently used, and I'm I intentionally did not say approved.

I'll mention that in a second. Because of the drugs that are currently used and the time it takes for most of those drugs to actually have a benefit patients that have FAP-associated desmoid tumors. I oftentimes, when I mention that surveillance and that active surveillance part, I oftentimes will start with sulindac or active surveillance because oftentimes there's pain and if I can get a response, I'd like to get that response in a way that in a situation where I'm given a drug that quite honestly, Motrin or sulindac, they don't have a lot of side effects.

So minimal side effects and the potential to shrink tumor or at least keep you from growing is really not a bad goal. Again, back to Dr. Hurley's discussion of resilience, setting expectations that many of the drugs that we use don't work quickly may lead to stable disease. And that, and really the discussion about what stable disease means.

And if we can keep things at a small, if we can keep a tumor small with a therapy that is well tolerated, that's a reasonable endpoint. If we think about patients that come to me understandably with cancer, want that cancer gone. I get that, but at the same time, we don't have an expectation for most other diseases in medicine that they're cured.

Patients take antihypertensive medications for their blood pressure for years or medications for diabetes for years. And if we can have tumors that are small, not causing symptoms with a therapy that has very minimal side effects, that can be a win. We look at if we look at a couple of the, these drugs in the category of tyrosine kinase inhibitors, there's two drugs that were shown to work in desmoid tumors at the same sort of, at the same conference around the same time. One of them is a drug called sorafenib. And sort of back to that point about the fact that, about approvals, sorafenib is a drug that is used to treat some cancers. Again, that's back to the point where desmoid tumors are oftentimes treated by oncologists because there's a consideration of using drugs that are treat, used to treat cancers.

There are no current FDA-approved drugs or desmoid tumors. And so if you were to say, Well, what's FDA approved at this point, the answer is nothing. And so we have drugs that in trials have been shown to be effective, but we don't have anything that's actually approved. If you look at the, if you look at the the data here, this is the drug called sorafenib.

This is data that was presented about four years ago. At one of our national meetings if you look at sorafenib, and this is the graph that we see here is

patients without events and the events is progression of their disease. So if you have a scan and then you do another scan, did the tumor get bigger?

And so, we're looking to see can sorafenib keep tumors from growing and if so, for how long? And you'll see that red line is sorafenib and very slow rate of progression for of their disease and placebo was much, much quicker. And now I'm gonna point out that this is a placebo control trial. And so placebos are things that we oftentimes think about that we don't often think about using in cancer trials, but in a setting where we don't have standard therapies that are available, things that are FD- approved, and given the fact that desmoid tumors can shrink on their own, it's appropriate to use a placebo in these situations. So if you're looking at this data and say, Well, of course it worked cuz it was compared to placebo. Placebo was a reasonable controller. If you look at upcoming trials and you say, Well, I don't know about a placebo, well placebo's a reasonable thing to do in this study I mentioned before, these don't work quickly.

This is a good example of that. Sorafenib here it took almost 10 months on average to get a response. When we think about FAP specifically, FAP specifically in terms of treatments compared to sporadic or spontaneous desmoid tumors some of the trials that have been done have not really differentiated.

And this is one of those situations. So it's not, it wasn't defined in this trial. How many patients had FAP. So we don't know necessarily how many patients were with FAP would respond. If you look at their response rates, how many patients responded? This is again, where we're looking at 33% of the patients had significant shrinkage of tumor that got sorafenib.

But back to that point about spontaneous changes in desmoid tumors, 20% of the patients had a decrease in the size of their tumor on placebo. Pazopanib is the other drug that is commonly used currently for desmoid tumors. In this particular trial, 13% of the patients had a a gene mutation is an APC mutation which is the common mutation seen in patients with FAP and 8% in the chemotherapy arm. Looking at sort of similar data 37% of the patients had a reduction in the size of their tumor.

25%. This was a trial that they compared it to a chemotherapy regimen 25% that got chemo. So even though it was a pill and not chemo patients responded more likely to respond. And again, stable disease, 59% of patients that got pazopanib had stable disease. And so overall a pretty effective therapy from a response standpoint.

And if you look at this graph, this is a type of graph. It's called the waterfall plot. It lists. So each of these bars is an individual patient. And if we were to look at if, look at the bars, if you look on the, that y axis, if you look at zero, that's no change at all. If you go up to 20%, that's kind of what the upper limit of what we consider stable.

If it's grows more than 20%, we call that progression. If the, if you look down on the lower part, 30% is what we consider within 30% stable. So anything above minus 30 is stable. But you can see there's a significant number of patients that were below that. So those are those patients that had response.

Again, back to the fact that these don't work quickly. You see the progression free survival is not reached at a year. So how about novel therapies? So interestingly the pazopanib and the sorafenib were both discussed at the same meeting. Just really quickly from a reason why we might hesitate to jump into those treatments quickly is they have side effects.

This is why I start with sorafenib, because pazopanib can cause things like high blood pressure. They can cause things like nausea, vomiting I'm sorry, nausea and diarrhea. That can cause fatigue. It can cause one's hair to turn white. They're not exactly benign. It's not an exactly a benign drug.

Sorafenib can cause fatigue and diarrhea. It can cause hypertension. It can cause elevated it can cause alterations in thyroid. It can cause thickening, blistering or blistering of the hands and feet. And so for something that patients might be on for a long period of time, that's why I would, I might start with something like sulindac and try to get control before I go to something like pazopanib or sorafenib.

And really because of the side effects more than the benefit, the rate of response is very similar. But the side effect profiles were, So this is where I will start with something simpler from a side effect standpoint. Two new things that have been discussed actually this month at a an oncology conference.

The data was presented this month. Nirogacestat and AL102. Looking at those, there's two trials I'll walk you through really quickly here. The nirogacestat trial is called the DeFi trial. Enrolled patients that had desmoid tumors that had the tumor was growing and either they could not have surgery and had not had therapy at all, or they'd had a prior therapy and a tumor had grown and patients were randomized and again randomized to the act, to the drug they were studying the nirogacestat or to placebo. And then they looked to see again, how soon the tumor would start to grow. Thinking back to whether this would

answer questions about whether patients with FAP might have a response in this particular trial, if you look at the number of patients with an APC mutation, 22% in the group that got nirogacestat, and 21% in the group that got placebo.

And then again, from an intraabdominal or extra abdominal location, or remember FAP normally intraabdominal 24 and 25%. So, certainly there was an enrollment of patients with FAP. If you look at, did it work the objective response rate, that's that complete response. Not anything on the scan or shrinkage of tumor more than 30%. 41% of patients that got nirogacestat compared to 8%, that got placebo and 7% of the patients had a complete response. If you were to look at patients that had stable disease as well, really significant benefits here, 50%, 34%, 7%. So over 90% of patients either had stable disease or complete response.

A little bit faster too. So I mentioned before about the length of time, 5.6 months until patients had a response. So this seemed to work faster than some of the other therapies that we've discussed before. This is, again, we've saw a graph earlier this graphs that looking at progression-free survival.

This is just sort of showing it the blue bar at the top is how quickly patients had progression with the nirogacestat. The black line is patients that were on placebo. And so if you look at this thing called the hazard ratio, that's the, that would suggest the risk, the hazard or risk of progression.

And in this case, the risk of progression was reduced by about 70%. So being on this drug about a 70% reduction in likelihood the tumor's gonna going to grow, did patients feel better? Remember I mentioned that sulindac really well tolerated. Sorafenib and pazopanib are not insignificant from a side effect standpoint.

This tended to be well tolerated. They did patient re they asked patients about symptoms. They did they did some some testing to look and they showed significant improvements versus placebo and reducing pain, which again, is one of the primary symptoms. Symptom severity was decreased and patients were more functional overall.

There was improvements in quality of life. So, a quicker response a a significant number of patients responding and patients felt better. There's another trial that was discussed as well. This is a a trial with a drug that's does not yet have a name. It's still letters and numbers. AL102.

Again, it's a very similar drug. I'll step back and mention that this is an entirely new category of drugs. It's something called the gamma secretase inhibitor. So as a category, that's kind of what it group it's in, it's a totally different class than the other two drugs, sorafenib and pazopanib.

This particular drug, AL102, has a very similar mechanism to the nirogacestat. A little bit different the way they were looking at their endpoints. There's this particular trial is not as far along. They have done an initial phase of the trial where they were trying to figure out what dose that was best to give to patients and they have said this was actually reporting of some preliminary data.

They are getting ready to expand this trial and do more patients at a, at the dose that was most appropriate. But in this particular trial, the interim analysis. At 16 weeks of therapy, they had nine patients at that po that point in time, one patient had a partial response. Again, that was more than 30% reduction.

Eight of the patients had stable disease, there was less tumor and seven of those patients. So remember I had shown you those graphs that showed like the number of patients have a reduction. All seven of the eight patients had less tumor there. And then at 28 weeks there were only three patients at that point.

And again, this is an earlier, earlier in the phase of this study, they're about to expand into a larger group. But at 28 weeks, so about half a year, three patients, there were two partial responses, and one patient had a, had stable disease. All of those patients had less tumor than when it, they were looked at when they looked at 16 weeks.

So essentially it may well be that, that they have not had optimal response yet. And so again, this is moving into a randomized phase. So they're gonna, much like the study I just talked about, they're going to be doing a phase where they compare it to placebo. So where do we need to go? So what are the future directions specifically for FAP-associated desmoid tumors?

Well, one thing, the current guidelines don't really give any guidelines for desmoid tumors that are due to the association with FAP. So I showed you a couple of trials where they've addressed sort of how many patients had FAP or the APC gene mutation. But we don't really have specific guidelines.

So in terms of the best therapy to pick it, we're not really quite sure where that's going to gonna fall. Are there novel targets? We know that the biology of FAP associated desmoid tumors is similar to sporadic desmoid tumors, but there is a unique gene and mutation. And then just from a biology standpoint, they're diff,

it's clearly different disease based on the way it presents in terms of location and things.

So can we find novel targets? Can we find other drugs that might work better based on a target unique to FAP? Is there a proper sequence for systemic therapies? You know, do we, right now with most desmoid tumors I'll either keep an eye on patients or use something that's has minimal effects side effects like sulindac then I'll move to the pazopanib or sorafenib, then I'll move to chemotherapy cause I'm increasing similar efficacy, similar benefit to tumor, but increasing levels of complexity from a side effect standpoint. If these gamma secretase inhibitors are approved that might change the sequence entirely because I might be much more likely to go really early to a gamma secretase inhibitor.

Cause I might be able to impact the tumor in a much bigger way, early in a way that's much more, more easily tolerated and it might work more quickly. If I have a patient that has a desmoid tumor in their abdomen because of FAP that's pushing on the small bowel and causing trouble, I might be able to get a more rapid response than I will with other therapies.

So I think there's gonna be a lot of questions about sequencing. And then we need to think about multi-modality care, and we're gonna be hearing about surgery next. Are there approaches where you do a cryoablation or a surgery to minimize bulk of tumor, have a decreased amount of tumor, but then sort of maintain things at a, at more of a steady stay or a stable state?

You know, so how do we use all the tools at our disposal to provide the best outcomes with the minimal adverse effects? So, with that, I am happy to take questions.

Jeanne Whiting: Dr. Shepard, I have a couple of quick questions here.

Dr. Dale Shepard: Okay.

Jeanne Whiting: One patient says, I'm confused. In the first presentation of the day, Dr. Pollack described desmoids as locally invasive, that have tendrils that can penetrate surrounding tissue. However, you mentioned that desmoids do not invade nearby organs. Wouldn't those tendrils be considered part of the desmoid and therefore considered to be able to invade nearby tissues/organs? Can you just clarify that?

Dr. Dale Shepard: Yep. Happy to. So that's a great question. So, I guess it, it would, it, when I say infiltrate and I tried to sort of describe it, I'll do that again cause it's an important point. And we're gonna get, we're gonna hear about surgery and so we'll get we'll get his opinion on this as well.

But when I say infiltrate so, if one imagines that another kind of cancer comes up against a bone, it grows into it becomes, it will eat away bone. We, when you think about metastatic disease, there's actually a hole in a bone. It actually eats into bone. So when I say infiltrate, I mean it actually goes, it would hit a bone and it goes right through it.

That, so, so the good, Dr. Pollack, So Seth is correct. There, it infiltrates in terms of these little tendrils, but it's really more following along a plane between two tissues. So when it hits bone, it doesn't grow into the bone. It goes along the bone and it grows along the sides, which is why oftentimes when our surgical colleagues take them out, and even though it looks like they're, it's out, they recur because of those tentacles.

So it doesn't grow into the bone, it grows along the bone. Does that help?

Jeanne Whiting: Yeah, I think that helps. And maybe the next speaker can even go into that more.

Dr. Joshua Sommavilla: I'll talk I'll be talking about that a little bit. I can comment now. I mean, the only thing I would add is that when it grows alongside those structures, there's also, there's often a pretty considerable inflammatory reaction and so they kind of stick together.

And a lot of the problems that can come from desmoid have to do with that relationship between them. Or though, even though it's not grossly invading it, it causes similar complications as if it were invading it, even though technically it probably isn't.

Dr. Dale Shepard: Which again, when we think about our sulindacs and non-steroidals, why those might actually have some benefit.

Jeanne Whiting: Okay. Yes, I was personally told they had to scrape it off my vertebrae, so that's not totally infiltrating, but somehow attaching as you describe it?

Dr. Dale Shepard: Yeah, it's, I guess I just meant that it's, it doesn't form large erosive changes like you would typically see with some other cancers.

Jeanne Whiting: Okay. I have another question that was submitted prior to the webinar.

My doctor told me I, I'm a sporadic desmoid patient been without any treatment for 15 years, but doctor told me with aging I could devalue, develop attenuated FAP. Is that true? Can a sporadic desmoid turn into some form of FAP and what is attenuated FAP?

Dr. Dale Shepard: Yeah, that would I guess, you know, they, I guess I'm not sure what terminology they're really referring to.

So, you know, FAP is its own sort of disease and set of complications, if you will. This is not something that someone would likely after a prolonged period, specifically with a spontaneous desmoid, if you realize that most desmoid tumors are in fact sporadic. You know, 80, 85% of desmoid tumors are sporadic.

So, patients with FAP are more likely to get desmoid tumors. The patients with desmoid tumors, that doesn't make them likely to get FAP. If I see a patient with a desmoid tumor, I wanna make sure that they don't have FAP. But it wouldn't be something that I would anticipate years and years later we would suddenly discover.

Jeanne Whiting: Okay. And finally, last question we have time for, Do you think we know enough about the genetic correlation of desmoids? I have had colon cancer, bladder cancer, and a mesentary desmoid tumor, but so far genetic testing is negative for FAP.

Dr. Dale Shepard: Yeah, I mean, I think there's, you know, quite honestly and you know, the medical geneticist could probably answer that better than I could, but I think there's a lot we don't know.

I mean, I think that as we learn more we can start making better associations between diseases and disease states and there's a lot of work being done in genetic susceptibility and genetic predisposition. When we look at rare tumors like desmoid tumors, you know, the, depending on what source you look at, there are, you know, a thousand or 2000 diagnosed a year.

There aren't large numbers to make good correlations somehow. You know, oftentimes, quite honestly, our family histories aren't as good as they should be. And so I think these are things that we might find you know, there may be a

gene correlation for those that constellation of of tumors that we just haven't identified yet.

Jeanne Whiting: Okay. All right. Thank you. Dr. Shepard, if you'd like to go into the q and a and answer some of the questions we couldn't present verbally, I'm sure they'd be appreciative. So, those questions will still be up. We'll turn the time now over to your colleague

Dr. Dale Shepard: Thank you again.

Jeanne Whiting: Thank you so much for your presentation.