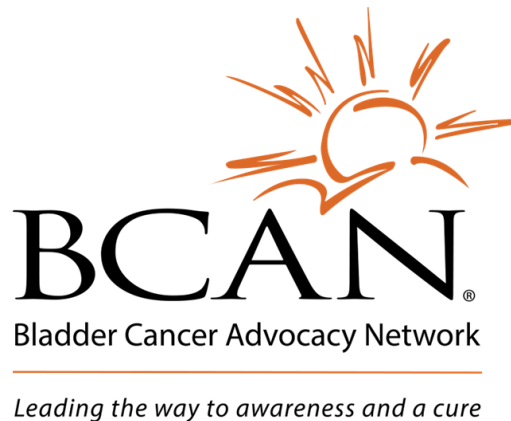


TREATMENT TALKS

What you need to
know about Clinical
Trials as Treatment for
Muscle Invasive
Bladder Cancer



Stephanie Chisolm:

Hello, and welcome to Treatment Talk, What You Need to Know About Clinical Trials As An Option To Treat Muscle Invasive Bladder Cancer. My name is Stephanie Chisolm, and I'm the director of Education and Advocacy here at the Bladder Cancer Advocacy Network. I want to remind everyone that as a participant, you're here in listen only mode. If you have any questions, please be sure you drop that question in the Q&A box at the bottom of your screen. And we will save all the questions for the end of the program and should be able to get through everything today. So ideally, when we join these programs, we have these Treatment Talks, for instance, this Treatment Talk about what you need to know about clinical trials as an option to treat muscle invasive bladder cancer, we have some general objectives. What we really want to do is help increase understanding of existing and new treatments, and in this case, clinical trials for the whole spectrum of bladder cancer diagnosis.

They're not just for advanced disease. And then showcase patient questions that you can ask to help empower you to be a good communicator with your healthcare team. And we highlight some current treatment advances for bladder cancer, keeping in mind, of course, that there are no new advances that are going to be approved by the Food and Drug Administration without clinical trials. I'd like to start just by thanking the sponsors of the treatment talks, the EMD Serono-Pfizer partnership, Merck, UroGen Pharma, and Bristol Meyers Squibb for their support. Today's program, What You Need To Know About Clinical Trials As An Option To Treat Muscle Invasive Bladder Cancer, features Urologist Dr. Karine Tawagi from the University of Illinois College of Medicine, where she's an assistant professor. Dr. Tawagi has joined the BCAN patient advocates, excuse me, joined by BCAN patient advocates, Alan Soles and Karl Pritchard, who both have participated in clinical trials. Hi Alan, and hi Karl. It's good to see you on here.

Patient Advocate Alan Soles:

Hi, Stephanie. Good to be here.

Stephanie Chisolm:

And Dr. Tawagi, thank you so much. You've got a great presentation. You're a urologist treating mostly non-muscle invasive and muscle invasive disease. What is the standard of care for patients with muscle invasive bladder cancer?

Dr. Karine Tawagi:

Sure. So I'm going to just share my slides here. Let me just pull this into PowerPoint mode. And just a quick correction, I'm actually a medical oncologist, but we work very closely with urologists. So I'll refer to where we as medical oncologist fit into the spectrum of treatment for muscle invasive bladder cancer. And so just an overview of how bladder cancer is diagnosed. So you may have blood in the urine or pelvic pain or burning upon urination, among other symptoms, that may prompt further investigations, including urine tests and blood work that may eventually lead you to a urologist. And the urologist, in order to diagnose bladder cancer, will put in a camera, also known as a cystoscope, you can see on the left hand side, into the bladder in order to visualize if there is indeed a tumor. So you can see, on the right hand side here, what a tumor may look like.

And then in terms of one urologist refers on to medical oncologists such as myself, these settings where we will see patients with bladder cancer are if they have what is considered to be high risk bladder cancer, also known as muscle invasive bladder cancer, or if they have cancer that has spread outside of the bladder, whether it's to lymph nodes or other organs. In terms of lymph nodes, those are part of the immune system, and they are these bean shaped organs. There are hundreds throughout the body. And often if a cancer spreads, that is one of the first places it spreads to. And I'll go over a little bit more terminology of what muscle invasive bladder cancer is. And so in order to determine if the cancer is muscle invasive, think of the bladder as having three layers, with the middle layer being the muscle.

So you want to find out how deep does the cancer go from the bladder into these layers of the bladder wall. And so the way that we find this out is through something called the transurethral resection of the bladder tumor, also known as a TURBT, which is something that the urologist will perform. So essentially, they will scrape off this tumor, and then they will find out how deep it goes. And the way that they can find out how deep it goes is by having a pathologist that gets the slides from the biopsy under a microscope and looks to see how deep this tumor may go. And so in terms of the stage of a bladder cancer, again, as you can see on the right hand, upper side here, this is what a bladder looks like, with the middle layer being that muscle layer as I mentioned. And we want to find out how deep does the tumor go.

So when you're looking with the camera into the bladder, you often can't tell how deep it actually goes, but these ones that are most high risk are the ones that invade into that middle muscle layer or beyond. And so in terms of how far these tumors go, sometimes we can't fully tell just by this camera and resection procedure alone. And so until the bladder is fully removed, sometimes we're not able to tell how deep does the tumor go. And so other ways that we can help determine how high risk a bladder cancer is by doing what is called a CT scan, or computed tomography scan. And on the left hand side here, you can see what a normal bladder looks like. So this big gray, almost square thing is a normal bladder. And then on the right hand side here, you can see what a bladder cancer may look like on a CT scan. So we can see here that there is a mass within the bladder.

And then we also do CT scans to determine if the cancer has spread outside of the bladder. And so in this case, you can see by the arrow here, that the bladder cancer, when they did the CT scan, appeared to have spread to a lymph node. And so this is important in terms of knowing what the treatment options may be. And so this talk is focusing mostly on muscle invasive bladder cancer, or these high risk

bladder cancers that are located within the bladder but may not have spread. And in terms of the result, if you remove the bladder, half of the bladder cancers invade to the muscle of, which 80% of patients survive long-term, a quarter of these bladder cancers both through the muscle to that third outside layer, and of those, 50% of patients survive long-term, but then a quarter of patients actually have bladder cancer that has spread to the lymph nodes, and 30% of those survive long term.

And so one of the problems is that we can't always reliably tell how deep the cancer goes, as I mentioned, but half of these patients will have the cancer come back at some point. And this is why patients are referred to medical oncologists such as myself in order to discuss treatments to reduce the chance of the cancer coming back. And so why do we use drug treatment and bladder cancer? So as we mentioned, we can remove the bladder by surgery, or we can also do radiation in order to eradicate the cancer in the bladder itself locally. However, cancer can spread both through lymph nodes or the lymphatic system, as well as through blood vessels. And so drug treatments can target cancer anywhere in the body, including cancer cells that you may not see to the naked eye on both CT scans or with that cystoscopy camera procedure. And so when do we add drug treatment? And this is what medical oncologists will manage. So we like to add drug treatment before surgery or radiation for those that are high risk.

And as we talked about, the high risk bladder cancers are the ones that invade into that muscle layer or beyond. There can also be consideration of drug treatment during radiation if a patient decides to have radiation instead of surgery, and then after surgery, for those that are high risk, there is also consideration of more drug treatments. And then for the patients in which the bladder cancer comes back, it's there's also many options for drug treatments. And so this is really a chemo approach in terms of how bladder cancer is managed. So there is chemotherapy which is managed by medical oncologists such as myself, and it can either be given before surgery, which is called neoadjuvant or after surgery, which is called adjuvants. There can be consideration of surgery to remove the bladder, and that procedure is called the cystectomy. And then there can also be a bladder sparing approach for select patients if they meet certain criteria, in which case they don't actually have their bladder removed.

They just have that scraping procedure where the bladder tumor within the bladder is removed, but they actually keep their bladder and get radiation to the bladder, along with chemotherapy. And so what is the standard of care chemotherapy for patients with muscle invasive bladder cancer? The most commonly used chemotherapy in this setting is something called cisplatin, and it can be given before or after surgery, usually in combination with another chemotherapy called gemcitabine. But one of the issues with this chemotherapy cisplatin is that there are many patients that cannot receive cisplatin for various reasons, including if they have many other medical problems, if their kidney function is decreased, if they have significant hearing problems, if they have significant neuropathy, which is numbness and tingling in the hands or feet, for example, some patients have this from diabetes, or if they have significant heart problems.

And then there are also other chemotherapies that can be given for patients that can undergo the bladder sparing approach, in which case they don't have surgery to remove the bladder. And so those patients get chemotherapy with radiation. And the names of those chemotherapies are called gemcitabine, 5FU with mitomycin C, and then cisplatin, which is the same chemotherapy I talked about in the previous slide. And then for those that have surgery, in the last few years, there was also the approval of immunotherapy, which can be given for one year after surgery. And this is called Nivolumab or Opdivo. And this has been kind of a new era of treatment in bladder cancer.

And so I wanted to just quickly mention, how does immunotherapy work? So we know we've had chemotherapy for decades and it's been used in many different cancer types, but immunotherapy has been a new treatment that has come out in the last decade or so. And basically, immunotherapy uses

your own immune system to fight off cancer cells. So your immune system is a collection of organs, special cells, and it recognizes cells that belong in the body. So cells on the left hand side, and then it also recognizes cells or substances that don't belong in the body, and it fights those things off. So that could be an infection, for example. So if you have a viral infection or a bacterial infection, your immune system will recognize that those don't belong. It will fight it off in order to clear the infection. The problem with cancer is that it's smart.

And so looking at this next slide, if you think of cancer as wearing a cloak in your body and floating around, your immune system doesn't see the cancer cells because the cancer cells are smart and are hiding from the immune system. And so one of the ways that we call this cloak signal is when this cancer cell has this receptor called PDL1 that binds to immune cells called T-Cell. And so the way that cancer can function in the body and grow is because your immune system doesn't see it. And so one of the ways that immunotherapy works is that it basically will decloak the cancer cell, and so your immune system can then see the cancer cells and fight them off. So here, you can see that the cancer cell is decloaked. So now your immune system or these T-cells can see the cancer cells and fight them off.

And these are the people that discovered immunotherapy, Dr. Allison and Dr. Honjo. And so they won the noble prize a few years ago for their discovery of immunotherapy. And immunotherapy is very successful in other types of cancer, including melanoma. So this is a patient with stage four melanoma, and you can see on the left hand side here. This is a PET scan, so the arrows here demonstrate melanoma tumors in the body, these black circles. And then the patient got immunotherapy. And four months later, you can see that all of those aero spots that demonstrate these melanoma tumors have virtually disappeared. And so how is immunotherapy being used in bladder cancer? So right now, there are clinical trials open to look at if immunotherapy would make a difference before surgery. There are also trials looking at immunotherapy, looking in combination with chemotherapy with radiation for patients that decide not to have surgery to remove their bladder.

And then after surgery, as I mentioned, there already is an approval for immunotherapy with this drug called nivolumab. And this was approved based on clinical trials that were done in the last few years. In terms of cancer that has spread outside of the bladder, we're looking at immunotherapy in the first line setting as the first treatment for someone with stage four bladder cancer, and it is already approved for patients in the second line setting. So there definitely is immunotherapy in bladder cancer. However, we're trying to see if we can get it approved in more places to see if we can have better responses.

And so what is new and drug treatment in muscle invasive bladder cancer? So we know that we have radiation, which is an option for some patients. We have surgery for some patients, we have chemotherapy. And then now, as I mentioned, we have immunotherapy, and also something called targeted therapy, which is being studied in this space. And chemotherapy can be very effective. So this is showing that, in a certain type of bladder cancer, chemotherapy reduce the chance of the cancer coming back after surgery by 51%. So we know that chemotherapy works. That is why it is the current standard of care in muscle invasive bladder cancer. But we are getting a better and better understanding of how cancer grows. And so these are just different pathways by which cancer grows. So cancer doesn't just grow usually by just one mechanism. There are many different ways that cancer can grow.

And so we're figuring out how in this cycle of cancer growth can we target the cancer in order to have even better responses than what we already have. And so I mentioned already immunotherapy as one of the ways that is being studied, but there are other mechanisms, such as fibroblast growth factor, which is also known as FGFR, which some patients have that have bladder cancer. And then there is also Nectin-4, which is basically like a little antenna on bladder cancer cells, and that is also being targeted as a new form of bladder cancer treatment. And so why clinical research? So only 5% of patients

participate in clinical trials, but really, it's the only way to continue to advance cancer treatment. And so if we have standard of care options, as I already showed you, why might a patient want to do a clinical trial? So some of the pros is that you can get access to the newest, most exciting treatments. You can have close monitoring the study because you'll have an extra contact within the cancer center in terms of research associates. That can be a great resource.

Some of the cons is that there may be a higher time commitment and extra testing. That the new treatments can have unexpected side effects. And having a trial doesn't assure that the new treatment will necessarily work, but it is being compared to the standard of care. And so what are current bladder cancer trials? So I showed you all of the different ways that bladder cancer can grow. So there are different drugs that are being studied in all of these areas to see if we can improve the outcomes. So that FGFR mutation that I talked about, so think about that also as an antenna that is on some bladder cancer cells. There are drugs that specifically target that antenna called Rogaratinib and Erdafitinib. There are also drugs such as Ramucirumab that are being studied. And then there are many types of immunotherapy that are also being studied, in addition to the Nivolumab, or Updivo that I mentioned. And some of those include one that is also very common called Pembrolizumab or Keytruda.

And then that other antenna on bladder cancer cells called nectin-4, there is a drug called Enfortumab Vedotin, which is being studied in this space as well. And so in terms of clinical trials in muscle invasive bladder cancer or this high risk bladder cancer that has a high chance of coming back, we have many clinical trials looking at immunotherapy with standard chemotherapy, or with some of these newer drugs. So these are just some of the names of the clinical trials that are ongoing right now and some of them are for patients that can get that cisplatin chemotherapy. And then as I mentioned, there are many patients that cannot get the cisplatin chemotherapy and there are other trials looking at these new treatments in those patients. And that is how we'll be able to have more options, is by having these clinical trials show us the results and change what the current standard of care is.

And so what is some advice for patients? So bring an extra set of ears, write things down, make sure that your voice is heard. It is a complicated decision for this muscle invasive high-risk bladder cancer. So oftentimes, the entire team will discuss the case and that includes the surgeons, the urologist, the radiation oncologist, the medical oncologist, such as myself, the pathologist that look at the slides under the microscope, the radiologist, the ones that read the CT scans. Make sure you ask for handouts in case you need to think about your decisions. Ask for alternatives and consider clinical trials. And so what questions should other patients ask about clinical trials if they're interested? So they can ask questions like, what is the purpose of the trial? Why do researchers believe that the treatment being studied may be better than the one being used now? Why may it not be better? How long will you be on the trial? What kind of tests and treatments are involved?

How will the doctor know if the treatment is working? How will you be told about the trial's results? How long do you have to make up your mind about joining the trial? Who can you speak to about questions you have during and after the trial? Karl and Alan shortly. Also, we can ask about possible side effects to the standard treatments, and then also questions about daily life. So how often will you have to come to the hospital at the clinic? Will there be any part of the trial that requires you to stay in the hospital? If so, how often and for how long? And then how often will you have checkups after the trial? So in summary, bladder cancer treatment is changing. Right now, chemotherapy is a really important part of treatment to reduce the risk of the cancer coming back, given either before surgery with radiation, or after surgery.

We have immunotherapies that are already adopted for stage four metastatic bladder cancer, and right now, it's being tested in about every aspect of this high risk muscle invasive bladder cancer in order to see if it should be added to chemotherapy or instead of chemotherapy. So it is important to consider

participating in clinical trials and communicate with your whole team about the best options for your situation. And thank you. Any questions?

Stephanie Chisolm:

That was wonderful Dr. Tawagi. So can you just tell us what got you excited and motivated to be involved in clinical research? There are plenty of urologists and medical oncologists studying bladder cancer out there. What triggers them to be researchers like you are?

Dr. Karine Tawagi:

So I think when you look at the number of patients with muscle invasive bladder cancer that have the cancer comeback, about 50% if you average everyone, and we want to really reduce that number. So if we can get those outcomes to be even better for our patients, the only way that we can really do that is by studying new drug treatments that can hopefully improve those percentages and odds for our patients, that they can live longer without their cancer coming back.

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