Stephanie Chisolm: Do we have any correlation with these after symptoms and treatment efficacy? Does it mean it's working if you're having these side effects?

Dr. Kukreja: Yeah, I don't think we know the answer to that. I think a lot of people have side effects means that your body's definitely getting exposed to the gemcitabine and docetaxel, but it doesn't, unfortunately, mean that the cancer that's in the bladder is sensitive to it and going to respond to it.

And if you are having symptoms with any of these treatments, I recommend that you talk to your provider. A lot of times we can give medications for nausea and that type of stuff. And for the lower urinary tract symptoms, a lot of times we can give medications to help get people through treatments for that too. So I think this just really emphasizes encouraging you to speak with your provider.

Stephanie Chisolm: Sure. Do you recommend giving BCG for six to eight, 10 years out assuming the BCG works? Does BCG just delay cystectomy? Or with high-grade T1 carcinoma in situ, is it possible to cure with BCG or just postpone the inevitable?

Dr. Kukreja: So, I think there's several questions there. So first question is, is usually we recommend maintenance for three years. There's a bunch of studies that were done quite a while ago, actually, that showed that with that induction, and then there's a maintenance course that goes for three years, that reduces the recurrences. I don't think there's any studies looking at six, eight, 10 years out with the BCG. If you're having recurrence at six, eight, 10 years out from the initial induction period and you responded the first time often we would just recommend doing a reinduction course.

As far as the T1 high-grade with carcinoma in situ, I think that when we talk about non-muscle invasive bladder cancer, that's probably one of the hardest combinations of non-muscle invasive bladder cancer to treat. I think anytime we have carcinoma in situ in there, those response rates are lower.

We recommend BCG for at least a year. For the highest risk disease there is benefit for up to three years, but this has not been studied beyond this time period. BCG can cure, but also may delay cystectomy. For high grade T1 with CIS, I often consider this the highest risk non-muscle invasive bladder cancer and it often has the lowest response rates to intravesical chemotherapy.

And depending on the size of the high-grade T1 and the extent of the carcinoma in situ, yeah, I mean, I think that cystectomy is often a reasonable upfront recommendation because this is the highest risk of progression. And this is a cancer that has obviously shown that it's aggressive and biologically has the ability, certainly, to progress to the muscle invasive disease standpoint.

The discussion that I have with patients that have this, if they have a big, high-grade tumor plus carcinoma in situ the issue is that if this progresses to muscle invasive disease while on BCG treatment, which there's about a 15% chance of happening, the survival rate goes down quite a bit. So somewhere between 60 to 50%, at five years, whereas if we get it while it's still in the bladder, looking at probably about a 90, 95%, five year survival rate. So that's a big change.

So, yes, it may be delaying cystectomy. Is it wrong? Not necessarily. But I think that you just have to have a really informed discussion with your provider on expectations and priorities.

Stephanie Chisolm: So this is a question that maybe Judy and Jay might have some experience with? Did you experience much pain with BCG? And if so, what did you find that worked best? We can go to Dr. K afterwards. But did you have any pain when you had your BCG installation?

Judy Walker: I really haven't had problems, as I have sort of hinted at before, that worried me a loss. Yes, there's burning after you void. You're supposed to keep it in your system for a couple of hours after you receive it, which is perfectly understandable. And then I felt, I don't know if this is the medical term for it, a general feeling of malaise. In other words, if I didn't get fevers, it was, as I said, a tape to my bed situation. And because I was told beforehand, that that was perfectly normal, I didn't worry about it. I just allowed time for it. So to me, I have been very lucky with respect to having very few side effects. Each time including at the beginning, I've been having I think for a couple years now I can't remember exactly, is that the next day I felt fine.

So for those people who are working, maybe Dr. Kukreja could answer this far better than I if people have different trajectories in terms of how they react. But I, personally, feel that an afternoon and evening of sleeping it off as a small price to pay.

Jay Powers: I agree for the most part with Judy, I did have some burning in frequency. But doctor prescribed a pill, I'm not sure what the medication was. And that eliminated that problem more quickly than just letting it run its normal course. So really, it was not very painful at all, but I'm still working. And I didn't like the frequency, the burning I can live with, but the frequency I didn't like to run to the [inaudible 00:43:10] so often. I'm in the construction business. So it was great that she had another pill that you could prescribe that would help me decrease the urgency.

Dr. Kukreja: So I was just going to say often we use antispasmodics. And those come in a whole bunch of different types of antispasmodics. A lot of them have side effects of dry mouth and some constipation. So we want to make sure that no constipation because that can make the treatment side effects worse. And then some people will use over-the-counter medicines or something like that. Most of the times those are most effective for like the bladder spasms and most of the pain after the treatments come from what we call bladder spasms. And it's not a true pain if you cut yourself type pain.

Judy Walker: I'd like to add one more thing that I think relates to something I wish I'd known a little bit earlier, but may have been told and forgot. So there's that. And that is that the timing and again, correct me if I'm wrong, but the timing to some degree and I've seen this in some of the materials too of getting your BCG treatments can be modified some. In other words, there are times when depending on the patient, I'm sure if you don't get it this week, it's not going to mess things up for you if you get it the next week kind of thing. And in my particular case, inevitably there was something else in my life being as old as I am where I needed antibiotics. And it caught me by surprise originally that there was a problem there with respect to taking antibiotics at the same time as BCG treatment.

Judy Walker: And so if I had just one suggestion for the cheat sheet that you get before you get BCG, it's those kinds of things for those of us particularly, we older people who take other drugs a lot to talk about the possible drug interactions and how those can be managed with BCG. That wouldn't have been on Dr. Kukreja's watch, that would have been the basic materials that you receive from your overall provider team.

Jay Powers: Yeah, I think the best thing is good communication with your provider.

Stephanie Chisolm: Okay. So I see Dr. Kukreja's answering some of the questions, but maybe some of them we can bring out to everybody because others might be thinking those questions. When you look at many of these intravesical therapies have a 50% success rate, how do you justify that? Obviously, it's certainly better than moving to the next more serious treatment. But in looking at weighing those pros and cons as you're making those kinds of decisions from a patient perspective, and also from a provider perspective, nothing is 100%. And then there are some people that don't respond to BCG. How do you process that? Jay and Judy, you want to start?

Judy Walker: Well, there is always, as Dr. Kukreja was saying, the chance that you're going to get really, really unlucky or you'll fall within a certain range. It's sort of like Mark Twain used to say, and I'll use the lowercase swear word, which is, "There are lies and darn lies in statistics." And you just have to figure out where you're likely to fall and play with the probabilities. And as Jay said, in close contact with your provider, as I said, and Dr. Kukreja told me to be honest. I have a tendency, forgive me on a retired attorney trained to think the worst at some level to prepare for a case with trial, for instance.

But that can be a mistake, because in the main, lots of people are a lot more fortunate than they think they're going to be. And I think it's better to find some happy medium with respect to how well you treat things. I don't think you should let anything slip by the wayside. But at the same time, you're not always going to be the one who has incredible bad luck. And I think that's a good thing to remember.

Jay Powers: And I think with any challenge you want to approach it in a positive mindset. And you don't know the outcome. Many of life's challenges are uncertain as far as the outcome is concerned, but with professional help and good communications, I think you can increase the odds of success just by being positive about the possibility of a good outcome.

Judy Walker: I parse that a little bit, given the fact that I have been taking an anti-anxiety medication that was for about six years, triggered by my husband's constant hospitalizations, and his getting a new liver and subsequent surgeries and all that stuff. And I completely agree that it's good to have a positive attitude, but I would just say, speaking for myself, that it's been great to have people

saying, "Okay, it's okay if you're really upset. It's okay if you're feeling really negative. It's okay, if you have these honest emotions."

Because I think in American society, we're too trained to be optimistic, and I would call myself a pragmatic realist. I want to know the truth. I think that knowledge is power. But at the same time, once again, sometimes freaking out is no joke. And it's really important to have a good provider team and have friend and family support. And if you can't stay positive all the time. Do not blame yourself for that. Do not blame yourself.

Jay Powers: Good point, Judy.

Stephanie Chisolm: When bladder cancer recurs, it comes back, how many times before you begin to think, "Well, maybe we need to move on beyond intravesical therapy." I know you definitely move on to a higher level of therapy when there's disease progression where it becomes muscle invasive, that's certainly a greater risks, but if you're just having annoying, non-muscle invasive tumors that keep popping back up, what do you do as far as being a provider, what are you thinking? And what are you going to suggest to a patient? How many times is too many?

Dr. Kukreja: Yeah, so I think there's a lot of nuances to risk. So, the carcinoma in situ that carries a particular higher risk than a lot of the other cancers of failing to respond to the intravesical treatments. So in patients with the carcinoma in situ I don't think that there's a one right answer to this question. And we actually we just discussed this in a panel at the Society of Urologic Oncology is when do you move on?

And for somebody with a T1 disease and/or carcinoma in situ, the consensus among us was usually we'll try one thing after BCG. So maybe we'll try gemcitabine docetaxel or pembro or maybe gemcitabine alone or mitomycin alone depending on what is in those areas. And if the bladder cancer fails to respond to that, usually, we recommend moving on to removing the bladder because the chances of progression in those patients are super high.

Now if we have a low-grade recurrence, and we just keep having low-grade recurrences, usually I'll try a bunch of different things. And I have not yet removed a bladder for just low-grade recurrences. So the interesting thing about non-muscle invasive bladder cancer is when does it come back? How soon after the BCG? How many places does it come back? What is the grade? What is the stage? Did the stage go from a TA to a T1? Did it go from a CIS to a T1? Is there CIS present?

There's so many factors that go into these decisions and recommendations. I don't think that there's one right answer for everybody. But I think when you have the highest risk disease, those are the patients we usually consider bladder removal.

Stephanie Chisolm: So if you've responded, BCG and maintenance has kept your cancer at bay, can you say that you're cured of bladder cancer? Or what do you tell patients?

Dr. Kukreja: So I always tiptoe around the cure. So, for patients that I do do bladder removal on that have non-muscle invasive disease, often I will use the cure word, because the chance of it coming back is so low. Patients that make it to five years, we usually say that whatever cancer was there, is

cured. But it can come back in other cells in the bladder. So whatever cells initially were causing the problem had been taken care of.

But bladder cancer is kind of what we call a field effect disease. So there are the same types of cells that something went wrong and in other places in the bladder, and up in the kidney and in the tubes that connect the kidneys to the bladder, the ureters. So we still usually keep tabs on patients, even though they may have finished their active and have no evidence of disease.

Stephanie Chisolm: Yeah, so those regular cystoscopy to take a look inside are really beneficial. There's not really any other way to determine if everything is still all clear, right?

Dr. Kukreja: Yeah, and also use urine cytologies, where they look at the urine cells underneath the microscope and CT scans. I think in the next couple years, we're going to see a lot more stuff come out with urine biomarkers that are somewhat better than the cytologies we use now. I don't think we'll have the cystoscopy need, but it may actually help us pick up things that we are missing in the kidneys and ureters portion.

Stephanie Chisolm: So it looks like none of the treatments have greater than 50% success rate after five years your chart shows BCG at 40%. Is this with maintenance? And then if so, when might removal of the bladder be inevitable? If it's going to come back, it's going to keep coming back. When do you make that decision? Is it just with disease progression or recurrence?

Dr. Kukreja: So yeah, five years is about 40%. But patients that respond initially to BCG, and everybody has a variable exposure to the maintenance, especially right now with the BCG shortage. So if somebody got an induction a year of maintenance and then they're recurrence at five years, I would try BCG again, unless there's like really aggressive features of that particular bladder tumor. Most of the time we talk about BCG reinduction.

And when people get those high-grade recurrences, the intensity of follow up increases again. So we do those cystoscopies every three months, the cytologies every three months, CT scans every year. So the idea is that we're keeping such a close eye on it that if it recurs, we catch it right away.

Stephanie Chisolm: Okay. So, obviously, we talked about holding the BCG or other installations in your bladder for a certain period of time? Do you have any suggestions for increasing the amount of time? Does it make a difference? Or what about people that can't hold the intravesical treatment as long as is required? Because for whatever reason, they just can't hold it that long? What do you do in those circumstances?

Dr. Kukreja: So there's definitely a group of patients that have problems holding the intravesical treatment. So a lot of times, what we'll do is we'll actually put a catheter in and leave the catheter in. And we hook it up to like a system where if they have a bladder spasm, the medication comes out and actually goes right back in to that dwell time that we need. I think each one has a different recommended dwell time. I think a lot of it was just the recommendations are based on what the dwell times were for the initial studies. I don't think we know if you hold BCG for 75 minutes versus 90 minutes versus in two hours, what the actual decrease in efficacy is. So everyone's different. But that's one of the things is we definitely don't know the answer to that. And then as far as like other things that I do, we can prescribe the antispasmodics. And sometimes we do something called out alkalinization

urine, that decreases the caustic effects of the chemotherapy. And sometimes people can hold it longer then.

Stephanie Chisolm: Okay, well, that leads me very well into the next question. Does cranberry juice or any cranberry supplement have a beneficial purpose or are they just a waste of money?

Dr. Kukreja: So it depends what we're talking about. So I do have a lot of colleagues that use cranberry extracts for recurrent UTIs. I don't think that there's any roles that we have looked at, in bladder cancer specifically, but for recurrent UTIs I do have a couple of colleagues that use it.

Judy Walker: I have actually tried them, because I thought what the heck? It can't hurt anything perspective on cranberry supplements. I can't remember if I actually talked to anyone. I couldn't take my own advice, right? And I got freaked out because it looked like blood or something when I was voiding. I don't know if there was actually a correlation there. But it made me more nervous than not as to whether or not I had a urinary tract infection or something. So on a cost benefit analysis, and I do think I talked to one of the nurses, a neurologic oncology about this. He just said, "Why don't you just cut it out?" And that's what I happen to do. That's my personal experience with cranberry supplements. They're gone.

Stephanie Chisolm: w more minutes, but I wanted to try to get a couple more questions in. What is the risk of bladder cancer post-cytoxan treatment for bladder cancer? I'm not exactly sure. The question is, what is the risk of bladder cancer post-cytoxan treatment for bladder cancer? I wasn't exactly sure. I think it's maybe in a recurrence, I'm not sure if you're using cytoxan.

Dr. Kukreja: We generally don't use cytoxan for bladder cancer. So it's also cyclophosphamide is the other name for it. A lot of times you will use cyclophosphamide for leukemias and lymphomas. It's part of the lymphoma protocols and stuff like that. The risk of bladder cancer is pretty low, maybe like one to 2%. There's other things that are associated with it, like hemorrhagic cystitis and stuff that can be headed off with other medications. So, in general, I don't... I'm trying to think of any variants for bladder cancer. For the most part we do not use cyclophosphamide for bladder cancer. So I would say the risk for other cancers, it's low. For bladder cancer, I'd say generally, I don't know a lot of people using it.

Additional information included by Dr. Kukreja: Yes cytoxan does increase the risk of bladder cancer, however we do not really know the specifics surrounding this. We do think that the Mesna now administered with the Cytoxan helps bind and excrete the compound that causes the bladder inflammation

Stephanie Chisolm: Okay, I'm going to go with one last question, because I think this is very timely. And you may not have the answer yet, because quite honestly, I don't think all of the studies have been done. But someone is going back for their follow up maintenance BCG in May. And they had a question about COVID-19 vaccinations. What are your thoughts on that? What should people ask their doctors as far as they're currently in treatment cycles? Are they at greater risk? We know that COVID is a huge risk. And we know that the vaccine has benefit. What kinds of things should they be asking about in terms of whatever you can think of off the top of your head, because there's not a lot of research, specifically relating to bladder cancer treatment and COVID-19 vaccine?

Dr. Kukreja: Yeah, so I think the first thing is that there's no biologic reason to think that the COVID vaccine will reduce the BCG efficacy, or that the BCG will reduce the COVID-19 vaccine. The first thing is that I think the efficacy is going to be fine with both of them. Where it's sequenced in your treatments, I don't know if it's going to make a big deal. I think it's very common to get fevers after both. It's very common to have after both. So I think a lot of the side effect profiles are going to be the same. So if you're one of the responders to BCG, that you always get a fever, stuff like that, you may want to schedule a little bit later. So you may not want to do them on the same day.

But I'm telling all my patients to get it. If they get the opportunity to get it, I'm telling everybody to get it. And we'll deal with the side effects. Whatever happens and whatever calls we got, we'll deal with all that. But I think if you have the opportunity to get it, I'm telling everybody to get it.

Dr. Kukreja: Yeah, and I think that's okay. Because those BCG treatments it's nine treatments in the first 12 weeks after you start it. So it's like the six plus three. So, a delay a week here and there is actually built into that. And it's okay if you delay a week for your BCG, that's fine. Just work with your providers and the office. And I can't imagine a provider saying for any reason that you cannot delay a week for your BCG.

What is considered BCG failure?

BCG is considered to fail a patient when the cancer never goes away, the cancer returns after BCG or if the BCG is not tolerated.

How many times should we use intravesical therapy after a recurrence before considering a removing of the bladder?

In general it depends on the types of cancer. For the highest risk bladder cancers, right away or after one round of BCG. Other cancers that are lower risk may benefit from additional treatments. I would recommend you talk to your doctor and healthcare team if you feel your current treatment plan is not working or you are scared of progression to muscle invasive disease developing while on your current regimen.

With the current covid situation, what will happen if in the middle of my treatment I need to quarantine?

It is okay if you miss delay a week or two because you have to quarentine. The goal is to administer 5 of the 6 treatments within a 9 week time period.

What is alkalizing the urine to get more dwelling BCG time?

It is giving bicarbonate pills by mouth to calm the bladder to be able to hold the BCG for longer. It changes the acid base balance of the urine to try to get the bladder to be less irritated by the BCG-but it still allows the medication to work

After the 6 treatments of BCG and failure, doc refuses to do another set of BCG treatments. I have 'CIS Refractory'. Suggests only surgery. Is this normal to not continue with a BCG treatment course?

Yes, when BCG does not treat the CIS, this is some of the highest risk bladder cancer. Cystectomy is certainly an option to consider. Other options may be pembrolizumab or gemcitabine and docetaxel intravesical treatments. Clinical trials are also usually available in this area. But a cystectomy is likely to cure the disease at this point.

Is there a problem if one has a UTI infection during BCG treatment?

No, it is common to have UTIs during BCG and it is okay to delay a week or two to resolve the infection.

Do we know of any correlation with these after-symptoms and and treatment efficacy?

We do not know if the systemic symptoms correlate with local response rates.