Dr. Ashish Kamat is a professor of urology and the director of the Urologic Oncology Fellowship at MD Anderson Cancer Center, and he's a graduate of the AUA Leadership Program. Dr. Kamat's experience is multidisciplinary management of urologic cancers with an emphasis on bladder and prostate and organ sparing therapies, minimally invasive techniques, and orthotopic bladder substitution or neobladder. He's a very busy surgeon and he maintains an active research portfolio to improve the care of his patients, and we're thrilled to have Dr. Kamat with us.

Dr. Janet Kukreja attended the University of Missouri, Kansas City, six-year combination program to complete her MD, and then she completed her residency in urology at the University of Rochester Medical Center in Rochester, New York. While she was in residency, she was able to earn her MPH from the University of Rochester School of Medicine and Dentistry, and she's currently a urologic oncology fellow working on clinical trials, health services research and translational research at MD Anderson Cancer Center.

Question 1: “I know that you mentioned something about having an immunocompromised partner, and I think that's a big question that we get on a regular basis. People are concerned because their significant other or someone in their home has a compromised immune system, and I know that people are just sort of tuned into this whole kind of germ transfer and everything when you have a compromised immune system, and I know you mentioned it in particular relating to sexuality, but are there other concerns of having somebody in the home that is on a BCG regimen if somebody they live with does have some serious compromised immunity?”

Dr. Kukreja: Yeah. I think the important thing is that, usually, your provider should be giving you instructions of how to dispose of your urine after the BCG is instilled, but the general principle is using bleach in the toilet to try and kill all those spores that may still be active and, with the precaution, that should decrease the risk of transmission to anybody that's immunocompromised.

What I would just add to that is that the use of bleach and all the other precautions are something that are in the package insert and, of course, a lot of doctors have to tell their patients about that, but the bottom line is those extreme measures, so applying bleach and using your own bathroom and things of
that nature are truly only needed if you have immunocompromised partners or family members, so very young children, most infants or very elderly parents or grandparents or someone who's actually immunocompromised because of disease, that is really the only instance where you need to take those extreme precautions. For the most part, unless there's direct contact with the bacteria, it doesn't really just get transferred from toilet seats or sharing bathroom or things of that nature.

**Question 2:** A patient was diagnosed with bladder cancer in 2016 where they had a six-centimeter tumor, most low grade, but small amount of high grade, and started BCG and went through the rounds, and then, in February, saw a small .5 tumor. They did a TURBT, and it was low grade, so, in May of '18, they did another cystoscopy. They have another cystoscopy coming up. If it's negative, should they start BCG again? They're a little confused on the protocol.

**Dr. Kamat:** It sounds from the information that you're providing to me at least that the patient was treated appropriately for a large tumor with some high-grade components and put on BCG, and the BCG was working, and it is working because it's keeping the high grade components from recurring, and a small tumor recurred, but that happens sometimes, so, yes, certainly, based on the information you provided, it sounds like continuing on the BCG maintenance is appropriate.

**Question 3:** How do you feel about the use of BCG with interferon?"

**Dr. Kamat:** It's not a matter of how I feel. It's a matter of looking at the data, and the reason that question keeps coming up is because there's a lot of publicity about Mike O'Donnell's BCG and BCG interferon combination trial in patients who hadn't responded to BCG initially, so I'll summarize it.

Really, in short, adding interferon to BCG doesn't really improve the efficacy of BCG in most patients, so that's what the data showed. In fact, in a randomized trial that came subsequently it was shown that adding multivitamins to BCG was just as effective as adding interferon to BCG.

That being said, if you really drill down and look at subsets of patients, there are some patients who do benefit from adding interferon, and it's a very tricky discussion that needs to be had one-on-one with the patient and their urologic oncologist, but, in short, it's some patients who can't tolerate a full dose and need to go to dose reduction pretty early.

There, the interferon does help. Patients who have a decreased immune response to BCG in the first place for whatever reason, there, interferon does help and, in patients who are not getting the appropriate cytokine release in their bladder, which is the substances that help with the immune response and killing the tumors, those are patients where interferon might help, so, bottom line answer, I use it. It works in some patients. It is not beneficial to most patients, and this is a complex discussion question which one should have with their doctor.

**Question 4:** "I've had three BCG sessions with three more in the initial six-week BCG treatment, I guess, coming up. I've had no noticeable side effects. Might that mean that it's not working as well as if I were having side effects?"

**Dr. Kukreja:** No, it actually doesn't. It's good that you're tolerating it so well, and it doesn't necessarily mean that you're not responding. You really won't know until about six months after the treatment, if you have another tumor or not, whether you responded or not. The side effects can be a good thing, but it doesn't necessarily mean that it's a bad thing.
In bladder cancer context, BCAN is the biggest resource. They list all clinical trials on their website, and they keep updating that. In general, for any cancer patient, or for, in fact, any other disease setting; clinicaltrials.gov website offers you the most comprehensive resource of clinical trials, which are open here in the US and abroad. All you need to do is just put in the disease setting which you are looking for, and then you can click on trials which are recruiting right now. You can then click on the trial and look for where the trial is open, and you can easily call the phone number listed on that page to find more about the trial and how you can be enrolled on that trial.

What I usually tell my patients is that if they are interested in some trials, they can go there, explore them, and bring in what they think is interesting to them; and I can help them decide what trial might be better for them, if they are going to travel for that regular clinical trial. Obviously, each cancer center has a certain number of trials which are open. For example, the Mayo Clinic here in Arizona, in bladder cancer we have four or five clinical trials open. We cannot open hundreds of trials because of the limited resources, and also, we have to assign resources to other tumor types. Different centers will have different trials. Some trials may be better for you, in your particular disease setting, and your physician can help you guide which trial might be appropriate.

**Question 5:** Somebody was really interested to find out about the statistics and what the data shows about the loss of effectiveness by using lidocaine lubrication, and then somebody else said that they’ve had lidocaine used with all of their catheterization, or hardly any lube at all. Some people are nervous about the mention that it is better to not use the lidocaine. Can you please discuss some of the statistics that might be showing that the lidocaine is not necessarily a good thing?

**Dr. Kukreja:** I can start with talking about the use of the lidocaine in general. It is perfectly reasonable to ask your provider not to use the lidocaine. I personally don’t know of a percent reduction in efficacy. I just know that the principle is based on the interaction with the lidocaine itself and changing the acidity of it so that the effectiveness of the BCG is decreased.

**Dr. Kamat:** Anything that’s acidic will decrease the efficacy of the BCG. Lidocaine is acidic, it’s well recognized. I know that they actually do a trial like this. We would have to knowingly put patients on an arm that is potentially less efficacious, so trials that have used lidocaine with BCG just haven’t been done because we don’t want to deny our patients the beneficial effects, so to answer your specific your question, no trial has been done using lidocaine because it is not something that’s ethical, number one, and, number two, if you absolutely can’t tolerate the BCG or the catheter instillation without lidocaine, then, obviously, you don’t have an option and you have to use it. It’s not going to abrogate the effects completely, but it can decrease the efficacy.

**Question 6:** The studies haven’t really been done to do a comparison, but patients get the sense that it is a better way to go, without the lidocaine. Is that correct?

**Dr. Kukreja:** Yes.

**Stephanie:** Are you saying not to take oxybutynin for spasms?

**Dr. Kukreja:** No. I think you should take it. If you’re having symptoms, it can be very helpful in symptom management. Any of the antispasmodic drugs, such as oxybutynin and ditropan, detrol, levsin, and hyoscyamine, all of those can be very helpful for you and are good if you need them.
**Stephanie:** Is it also okay to use ibuprofen if you have any symptoms?

**Dr. Kukreja:** Yes, that should be okay.

**Question 7:** If a patient takes his cholesterol medicine in the morning, is it okay to take cholesterol medicines before the BCG treatment?

**Dr. Kukreja:** On the mornings of the BCG treatment you would want to just switch that to after the BCG treatment so it's not in your bloodstream.

**Question 8:** “I finished my first initial first-time induction of BCG in February, and had no side effects at all. Is it a myth that BCG didn't work here? The reason being I noticed darker urine, maybe some blood, not sure, in the last few weeks. My six-week scope is next week. Should I be worried?”

**Dr. Kamat:** I know it's impossible for me to really answer that, but what I would say is it doesn't necessarily mean that the tumor is recurring, but it is something that they should let their provider know and, if they're having a cystoscopy coming up pretty quickly, they'd be able to detect it.

**Question 9:** “I initially got diagnosed with bladder cancer, had TURBT and biopsy, diagnosis of pTa high grade, and I had initial induction of BCG followed by another TURBT a few months later with the biopsy showing carcinoma in situ, followed by another induction of BCG, additionally with interferon. This time, that resulted in the "emission of CIS," but I'm not sure what that means; then I had four maintenance courses of BCG and interferon, showing no CIS. However, most recent biopsy shows CIS is back. What are my options besides a radical cystectomy? I'm scheduled for induction of mitomycin soon because my urologist thinks it's okay since BCG did cause a remission for so long, but I'm wondering is it better to go ahead and do the radical cystectomy? I know you can't give advice, but what are your thoughts? Does it make sense to try at least one more round of intravesical treatment before considering the radical cystectomy?”

**Dr. Kamat:** I'm happy to answer this with a disclaimer that I'm going to answer it in a hypothetical fashion and not give actual medical advice, but if somebody presents in this manner where they have a high grade papillary tumor and they also have carcinoma in situ at the same time or at a subsequent biopsy and then they respond initially to BCG or BCG plus interferon and then have a recurrence of carcinoma in situ, which is high grade, it's not as benign as CIS in some other organs.

In the bladder, it's high grade, it's dangerous, and it can actually metastasize and kill our patient, so if they have a recurrence of carcinoma in situ while they're on the BCG, that puts that individual in the highest risk category of having an adverse outcome from their bladder cancer, if they continue to try to spare the bladder without the proper precautions, and that's the reason that all the guidelines and most practitioners will recommend to the patient that, at this point, you should really strongly consider having your bladder taken out.

That being said, most patients will say, "Well, I want to try at least one other thing, and let me try something else." It's not unsafe to try an alternative therapy so long as there's a defined plan in place, which means don't keep trying therapies until the tumor gets so out of hand that you can't be cured, but if you want to try one more treatment option with the understanding that if that doesn't work, then in three months or six months, whenever the tumor recurs, you will agree to have your bladder taken out rather than try to clutch at another straw.
It's definitely worth doing that. Again, it's a risk-benefit ratio, but I would strongly recommend asking your provider if he or she has access to clinical trials because there's a lot of clinical trial agents that look like they have much better efficacy than mitomycin alone, which really doesn't work in that situation, and if they don't have access to clinical trials, then a single agent chemotherapy. It's a single drug, whether it's mitomycin alone or gemcitabine, or a single drug really doesn't have more than an 18, 20% benefit.

Combination chemotherapies do have more of a benefit. There are some data to suggest that if you combine gemcitabine and docetaxel, you can get 54, 57% response rate, but, again, this is a hypothetical discussion. I would strongly recommend that you talk about these options with your urologist, but it's not unsafe to try one last thing before the bladder is taken out.

**Question 10:** In general, what is the recommendation if BCG failed and then there is a recurrence? What's the next step?

**Dr. Kamat:** If BCG fails and truly doesn't work, then a radical cystectomy may be done. If someone is averse to radical cystectomy or, unfortunately, is too sick or not able to undergo the surgery, then he or she could try other alternative therapies.

There are some data to suggest there's a trial that's looking at radiation therapy as well. Older data suggests that it doesn't really work well, so I would be hesitant to recommend it unless the trial shows positive results, but that is an option for some patients, too.

**Question 11:** “I've heard about staying on BCG for the rest of my life. What do you think about that, staying on the protocol for the rest of my life?”

**Dr. Kamat:** Yes, so that's a question that is actually based in science, so there's a reason for people to have heard that. Essentially, it's thinking about the immune system and the fact that you need to have a tetanus shot every ten years, or to get a hepatitis re-vaccination every so number of years to keep the immunity going. It's the same thing with the bladder, and patients who are fortunate enough to have responded well to BCG, but sometimes do need to have a re-boost with the BCG. Whether it's every year, every other year, every three years, nobody really knows because the studies haven't been done, but the reason that some urologists will talk to their patients and say you should get a boost every year or every two years is because they're trying to re-challenge the immune system and keep it stimulated so it fights the tumor.

**Question 12:** Please repeat the Lamm Protocol or maybe explain the difference between the Lamm Protocol again and the SWOG Protocol.

**Dr. Kamat:** There's no difference. The Lamm Protocol and the SWOG Protocol are one and the same. They're just called different things in different parts of the country or internationally, so the "6+3" Protocol is essentially called a SWOG Protocol or the Lamm Protocol in many parts of the world, so they're just different terminologies for the same "6+3" regimen.

BCAN staff mentioned that there's a really good explanation of that in our Expert Explanations document. There's even a page where you can keep track of all of your treatments, and you can just cut it out and fold it up and put it in your wallet if you’d like to do that, so we try to make it as useful as possible for you.
**Question 13:** “Number one through number 10 were somewhat uneventful. Number 11 and 12, were bloody with minimum amount of pain, but the urgency was just out of here. What does this mean or why was it so bad? I did hold number 11 treatment for two hours, 45 minutes due to the fact that I just couldn't get home. Could that be a reason why there was more pain and perhaps more blood?”

**Dr. Kukreja:** Yes, so the longer the BCG makes contact, sometimes, some people will have more irritation. I guess the question that I would ask is about the bloodiness, so most people wouldn’t have very bloody urine afterwards, so if you're having very bloody urine after the instillation, you should talk to your provider, and, also, if you are anticipating that you’re going to have symptoms, you can also take those medications that we talked about, those antispasmodics, before the procedure, too, and you can talk to your provider about that and tell them, ”I really have a lot of spasms right after I got the instillation last time. Is there something I can take before I get it so that I can tolerate the instillation?"

**Question 14:** Why does a doctor only recommend two years of BCG treatment; why not ask for three? Why are some people getting six BCG treatments and others don’t? What should we really be asking our doctors? How should they bring it up to their doctor to figure out how long they should be on BCG?

**Dr. Kamat:** Essentially, they just need to have an open discussion with their urologist and let their doctor know that they are aware that a six-week instillation, meaning six weekly instillation of BCG, once a week for six weeks essentially, is an induction course and that the maintenance course is once a week for the three weeks, and that's given at three months, six months and every six months thereafter for three years.

Too much BCG is bad for you, so just going on and getting six weeks of BCG every time is not good. The three-week is optimal, and if they go or veer away from the schedule, they just need to ask the urologist, who may have a reason. They may feel that the patient is reaching a point where they won't be able to tolerate the side effects, or they may have other reasons for it, so not everything is done without a reason, and they just need to have a discussion with the urologist.

Similar to the BCAN handout, my nurse, Prasanth Abraham, was very instrumental in creating that kind of like a cheat sheet for our patients because it's hard for patients to keep track of their BCG, and this is really useful if they print it out and take it to their doctor’s office and, essentially, every time one gets a BCG, they could themselves either sign or initial it and put a date in there. It will help them and their doctor’s office keep track of their BCGs. Just practically speaking, sometimes people forget and they end up skipping a BCG because they forgot to make an appointment. This would prevent that.

BCAN staff encouraged the participants to please download the form. There's also the plain language “Get the Facts,” where there are tips from other patients on what they wished they had known before, during and after, so those two pieces might be very beneficial.

**Question 15:** Is BCG effective on patients that are on anti-inflammatory regimens for autoimmune disorders or perhaps have rheumatoid arthritis? Is it as effective in that population?

**Dr. Kamat:** That's a broad question. The bottom line answer here is that BCG works and it works across the spectrum of patients. The more immune-suppressed somebody is, so there are some patients who are on anti-inflammatory medications for rheumatoid arthritis, that is really severely immunosuppressive, and for those patients not only would BCG be much less effective, but it potentially...
could cause an actual BCG infection because those patients are really immune-suppressed. If someone is on a really high dose anti-TNF type medication, they would know. Their rheumatologist would have told them, "Just don't get any dental work done without checking with me," et cetera, et cetera, but if someone's on routine anti-inflammatory medication, they can get BCG, but it might decrease the efficacy just a little bit.

**Question 16:** If a tumor is low grade or high grade, can the urologist look at it through cystoscopy?

**Dr. Kamat:** I was just going to say that's a yes and no answer. If you looked at 10,000 tumors, you get a good guesstimate as to what the tumor looks like, whether it's low grade or high grade, but the only way to prove that for sure is to do a cytology and a biopsy. This is a little less of a concern in patients who've had low grade tumors for a long time, and those low grade tumors pop up. They tend to remain low grade. It's uncommon for low grade to go to high grade, unless there's a dramatic change in size, et cetera, and, oftentimes, in patients who have low grade tumors, the urologist may look at the tumor in the office and say, "This looks low grade. Let me just cauterize it," rather than put you to sleep and put you through the whole anesthetic, and, there, it's very appropriate because if a patient has had low grade tumors multiple times in the past and it looks low grade, in that situation, most urologists, close to 95, 99% of the time, will be accurate.

**Question 17:** Is Blue Light Cystoscopy useful for follow-up cystoscopy to pick up more tumors that might not be visible on the regular cystoscopy?

**Dr. Kamat:** Blue Light Cystoscopy does pick up more tumors than is seen with White Light Cystoscopy. The long convoluted response is that it's not available yet in the US for use in the clinic. The trial was done. FDA needs to go through its process, and eventually it will be available, but, right now, it's not available for use for follow-ups. It's only available for use for actual resection because the patient has to have a Rigid Scope, and that's usually done under anesthesia.

**Question 18:** “Why is my NCI urologist not giving a TB vaccination along with BCG? I read that Dr. Lamm recommends that. I know you can’t speak about one particular doctor, but is that the protocol? Is that generally what people should do to make sure that somebody has the TB vaccination?”

**Dr. Kamat:** No, so the reason Dr. Lamm and others have sometimes recommended that somebody gets a TB vaccination intradermal is the observation that patients or people who have been vaccinated against tuberculosis in different countries, such as India and Europe, essentially, have a higher response to BCG. It’s not something that's actually been shown in any large-scale studies, and there was a study ongoing in the US right now actually. One of our former fellows is now a professor at University of Texas, San Antonio, Rob Svatek is leading it, and their patients are being randomized to TB vaccine with BCG versus no TB vaccine and BCG, and that should answer the question definitively. It's not standard therapy. It's not recommended in any guidelines for the simple reason that it hasn't actually been proven, although, mechanistically, it makes sense what Dr. Lamm was recommending to this particular patient.

**Question 19:** Do you know if there are any interactions of BCG with herbal remedies? That's kind of a tricky question because herbal remedies could be all kinds of things, and so do you know if there's any
evidence that it doesn't do well if people are trying other kinds of remedies that are not things that are prescribed by their doctors?

**Dr. Kukreja:** I think that it's important to discuss with your doctor if you're taking herbal remedies. Unfortunately, there is not a lot of data on herbal remedies interacting with most medications, and BCG is one of them. We don't really have any data on herbal remedies and the interactions with BCG, so that is a discussion you should have with your doctor, but, in general, staying away from things that you don't need is probably the advice I would give you, but it has to be an informed decision between you and your doctor.

**Question 20:** If you need to postpone or stop your intravesical BCG treatment because of fever or some other reasons for one or two weeks, how do you get back on the cycle? How do you plan the treatment? Do you start a new six weeks of therapy or do you just continue the treatment after the gap as it was already laid out?

**Dr. Kamat:** It really depends upon why the individual had to postpone their BCG therapy. If it was because he or she was having a little bit more side effects and they had to skip a week, then getting right back on the regular cycle is perfectly appropriate.

If it was a longer duration, say, because somebody unfortunately had a heart attack, had to have a cardiac stent or something put in and just got delayed and derailed and there was a long gap of three, six months per se, then, sometimes, getting a re-induction may be required, but unless the gap is really long, just getting back on the schedule works, but the key question here is why was the delay, and if the delay was because of side effects, then you don't need to necessarily get back on the schedule because your doctor will modify the schedule for you.

Modifying the schedule for an appropriate reason is perfectly valid, which is why I emphasized earlier that if you download the schedule and you follow it, that's great, but if your doctor varies from it a little bit, it's likely that she or he has a reason. You just need to be aware that there's a reason and it's not simply because an appointment was missed.

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