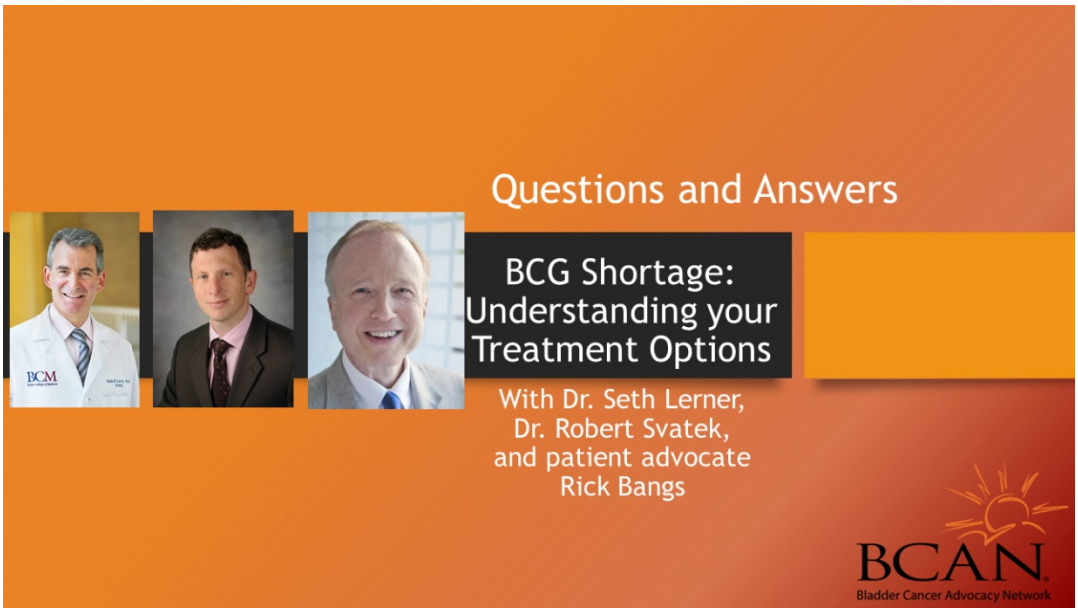

Questions and Answers about the BCG Shortage

Stephanie C: So now I'd like to open it up to questions from the audience. A number of questions have already come in. Many of them we've actually already talked about. But I'm going to try to go through some of these so that we have a chance to get to as many questions as possible.

Stephanie C: The first question that I wanted to ask the group is that if you went through the first six weeks of BCG and now it's not available, what alternatives do you have? I know you've talked about that somewhat, both Dr. Lerner and Dr. Svatek, but can you just mention again what can happen if you've already gone through the first six months but you can't get anything for the maintenance, what are your options?

Robert Svatek: The first thing I want to say is that I think most of us would agree that those first six weeks are the most important. Not to say that maintenance is not critical, but the fact that you're able to get the first six weeks is encouraging. I think that Dr. Lerner outlined some of the ideas out there for treating in a setting where you don't have access, so split dosing, getting half or a third, sharing it with other patients in the clinic. Some urologists' practices are doing that. That's an option. Using gemcitabine, mitomycin, docetaxel instead. Is it safe to not get further BCG and just wait? That would be a discussion you would have to have with your urologist. In general, most patients that are getting induction BCG are high-risk. It would probably not be safe to not get anything at all, but this is something you'd want to discuss with your urologist.

Stephanie C: There was a question that concerned any research that shows results if the one-third dose is used each time in treatment rather than the full treatment. Can you talk a little bit about what patients can expect if they're able to get at least the one-third dose.

Seth Lerner: I'm happy to help with that. There was a clinical trial that compared full dose BCG and reduced dose BCG plus maintenance in both what we call intermediate-risk and high-risk disease, and it affirmed the need for full dose BCG for three years in high-risk patients while and since it also addressed intermediate-risk that as I mentioned before we're strongly advising urologists not to use BCG for intermediate-risk. Full dose would be the standard of care if we had adequate supplies of BCG. I think that there is a pretty strong consensus, and I think the joint statement reflects that, for patients who are just starting BCG treatment, this induction, that we want to give them full dose BCG wherever possible and not reduced dose. Those patients are prioritized. As an aside, we'll often reduce the dose of BCG to manage side effects. We have a lot of tools available to try to get people through the side effects of BCG. But one strategy is to reduce the dose. So it's not uncommon say during those first six weeks of treatment that we may reduce the dose of BCG even though full dose is the standard of care. And then sometimes what happens as people move on through their maintenance courses that the side effects of BCG are significant enough that we'll reduce the dose for those patients. I think in a perfect world, we should prioritize induction BCG in that first three-month maintenance to get full dose, then as needed, reduce the dose. The question really was, do we know whether reduced dose is as effective? I think the answer to that is possibly. We know that in patients who have immune memory from that induction course that with even by the second maintenance treatment that immune response can be quite robust. And you can achieve that in certain circumstances with reduced dose. But I would say that reduced dose BCG would be better than no BCG at all. Whether or not a given patient is going to do as well with reduced dose or not really is going to be very patient specific.

Seth Lerner: Rob, I don't know if you have different points of view or anything else you can shed light on regarding the efficacy of reduced dose.

Robert Svatek: Yes, I think you stated it pretty well. I agree with your comments, especially the point about reduced dose. I think we all feel that a reduced dose is better than no dose. I just agree with everything that you said.

Stephanie C: Another question. Somebody had gone through their entire treatment and is now scheduled for maintenance BCG but obviously that's not an option and their urologist basically said that periodic scoping is a better option than the alternative methods, which are not as effective. They were looking for your thoughts on that. Just going back for periodic scopes to see if the cancer has recurred, is that better than some of the alternatives do you think?

Robert Svatek: I think the periodic scoping is required no matter what. This is the standard of care for patients with high-risk bladder cancer is to get a cystoscopy every three months for the first two years after their tumor removal. There is some flexibility with that and certainly in intermediate-risk or lower-risk patients, that is flexible. But every three months for the first two years in high-risk patients, that's done regardless of whether or not there's treatment. The cystoscopy itself, looking in the bladder, is not treatment. It's just to diagnose and to identify any relapses.

The real question is, what they're really asking is, is it okay to not get any type of maintenance therapy. And that was kind of like the first question. I would say in certain situations some of my patients, I have said, "We're not going to give any BCG and any gemcitabine, and we're just going to watch you and do cystoscopies." In some patients that's okay. In higher risk patients, I'm less comfortable with that, and I'd rather them get some form of chemotherapy. Seth would you agree with that approach?

Seth Lerner: I don't think we have a lot of data on mixing treatments in that respect. I think that it depends upon how concerned the urologist is about the risk of the patient recurring and where they are in their treatment. So for instance, I had a patient whose been on maintenance and I got him out to two years. He's done fine. He's never recurred, but he is having some side effects. And I said, "Look, I think we're just going to stop," even though he'd be due for two more rounds of maintenance therapy. I think there's ways you can do that. I guess the question is if you got a patient through induction and they had an initial complete response and you don't have enough BCG for maintenance, would I do anything else at that point. I don't know to be honest with you. We obviously know that more BCG at maintenance is better than induction alone. I'd just try to manage that on an individual basis.

But I'd have no qualms if someone said, "Okay, we don't have any more BCG. Let's give you a round of intravesical chemotherapy and then do maintenance there." We're all going to have to be creative and use our experience and skill set to individualize patient management. I think the other thing is that all general urologists go through training and understand how to treat bladder cancer. They may not be as adept at and having the flexibility with someone that has a lot more experience so encourage your doctor to reach out to an expert in one of the academic centers if they have questions about what to do.

Stephanie C: Terrific. Here's a good question. If you've been on BCG and now have to substitute with chemo, can you go back on BCG when it becomes available again?

Robert Svatek: I'd say yes. The short answer is sure. I think the other question is should you? I guess that depends on how long it's been since the tumor relapse. For example, like the scenario that Dr. Lerner described, if somebody's gone two years without having any relapse and we take them off BCG because of lack of availability and they go for another year without having any disease relapse, I think most of us would not recommend starting BCG back up. That patient may have, for all purposes, been cured. It is a case by case basis. We don't have data that would say that if someone's been on gemcitabine or mitomycin or other chemotherapy agents that there's now some increased harm in starting BCG back up again. I think it's just a matter of are the potential side effects and downsides outweigh the potential benefit. That would be again an individual basis.

Stephanie C: Thank you. Our next question, “I have T1 and carcinoma in situ high grade and USC no longer has any BCG and UCLA is giving the one-third dosage. Can you go back to that definition of where this would be beneficial?”

Seth Lerner: I made the comment that some BCG is better than no BCG. I'm not, and I don't want to sound critical of what other people are doing ... I'm not intending to do that. But I'm just wondering, Rob, if the choice was one-third BCG versus say gemcitabine/docetaxel, I might go with gemcitabine/docetaxel. What do you think?

Robert Svatek: I'm not sure. That's tough. I do want to clarify ... with T1 high grade CIS, this is high-risk. This is a high-risk tumor. Ideally, this patient would have a re-resection where they go back and re-resect the tumor. I have a patient like this that I have resected now three times, and we're planning on another resection. We're hoping that BCG is going to be available in a month or so. Again, I'm not advocating this is standard therapy. We're taking it on an individual basis, but clearly this patient has high grade and high-risk bladder cancer. The treatment of choice, the recommendation is re-resection of T1 disease to make sure that there's not more extensive involvement of the muscle for example followed by induction BCG. And that would be

the treatment of choice for this patient. I would encourage this patient to see if a clinical trial might be available nearby.

Stephanie C: Great. So in this era, is gemcitabine or mitomycin-C the preferred intravesical chemo agent? Is there anything in the literature that says that one is better or perhaps less toxic than the other with the same effect? Is there anything that you can comment about that?

Seth Lerner: I'm not aware that the two have been compared head-to-head. What I am aware of is that mitomycin is a standard of care for patients with what we talked about previously, intermediate-risk disease and that there was an elegant study that was published many years ago, in 2001, that showed an optimized way to give mitomycin. When that regimen is followed, it can be a very effective intravesical chemotherapy drug, particularly for patients with intermediate-risk disease.

Gemcitabine, we've developed a lot of experience with in a variety of different settings. For instance, in the patients who are no longer responsive to BCG. We use it in the perioperative setting. I think some urologists are using it as an alternative to mitomycin. Perhaps there's a perception that it's a bit better tolerated. But I think both are good options. There's no data to show that one's better than the other necessarily. What I would do in that setting, if a patient was seeing me, is we would use this optimized mitomycin-C regimen and monthly maintenance, and then if they recurred after that and still have intermediate-risk disease, gemcitabine would probably be my next choice. And I might even go with a combination of gemcitabine/docetaxel.

Stephanie C: There's another question here. Can I go outside the United States to get maintenance BCG with another strain, such as the Tokyo strain? And how would somebody go about doing that? Do you know that?

Robert Svatek: First of all, the TICE strain that we're using in the United States is being delivered through many other countries. So for example, Canada, you're going to have the same issues that you'd have here. And there's probably a lot of European countries with the same issue with supply and demand of TICE. I don't know how this would be done. I don't how exactly the logistics of it. Is it possible? Yes. The Tokyo strain is currently used in Japan. There is a different strain that's used in Brazil. These countries are using other strains. Perceivably possible, but exactly the logistics of setting that up is not something that I have the expertise to guide you on.

Stephanie C: Thank you. We do know that Merck has said that they are still working to try to rectify this problem. They anticipate the shortage was going to at least last a year. It is a long lead time to produce BCG. Isn't it a few months from start to finish? Everything needs to be perfect in order for the batch to be usable. Is that correct, doctors?

Seth Lerner: Yeah, that's well said.

Stephanie C: I'd like to thank everyone now, as this concludes our program. We want to give you an opportunity as well to sign up for additional alerts. So all of that is in the email, and it refers you to our website. Again, I would like to thank you very much Dr. Lerner, Dr. Svatek and Mr. Bangs for all of your insight on this. This has been incredibly helpful. This is a tough time for the bladder cancer community, but we absolutely appreciate you sharing your expertise with us.