



Maximizing your Treatment and Alternatives to BCG

Robert Svatek: Seth Lerner has been working with the AUA in terms of creating guidelines on how to handle shortages and maximize treatment options in situations where there is a shortage.

Seth Lerner: This is a real challenge, and there's a fair amount of variability from one site to another, in perhaps different regions of the country and say for instance, in our case at Baylor, how much we had on hand at the time that this shortage really began in earnest. Some sites, some doctors may actually have enough BCG at the moment and even with allocations and limited supply moving forward, are able to stay ahead of things. And then the other thing that you'll hear a little bit later is there's an opportunity for clinical trials that provide BCG or an alternative to BCG, and an individual patient's eligibility will depend upon the grade of their cancer, whether it's a first occurrence or a recurrent cancer, if they've had BCG before or not. In the midst of this BCG shortage, clinical trials really provide an opportunity for alternative treatment strategies or other approaches to immunotherapy, which is how BCG works.

The slide has a dark grey header with the text "Where can you find BCG?". Below the header is a light grey background with a bulleted list. The BCAN logo is in the bottom right corner.

- Supplies vary by site and time
- Other urologists or institutions may have sufficient quantities
- You may be eligible for a clinical trial that provides BCG or an alternative to BCG

How you can help ensure BCG is available?

- Speak out
- Contact your elected representative
- Visit www.bcan.org/2019-bcg-shortage-bladder-cancer for updates and sign up to receive advocacy alerts.



Stephanie C: Before we get to the AUA guidelines, here is a quick note from BCAN. We want to do our best to help ensure that BCG is available, and BCAN is speaking out. We have some information that is available if you want to contact your elected representative to let them know how you're being impacted by this and again, you can go to the website and sign up to receive advocacy alerts.

Seth Lerner: At a meeting where pretty much all the stakeholders, including BCAN, were present at the table. We had with us representatives from Merck, the American Urological Association, the Society of Urologic Oncology, Large Urology Group Practice Association and NCCN guidelines in addition to Rick Bangs, Dr. Svatek and myself. We, subsequent to that, issued a joint statement which reflects what I'm about to go over right now. My personal sense of this is that if urologists consistently will follow these guidelines, then I think that this shortage will be hopefully short-lived and the supply will meet the demand by having modified and decreased the demand as I'm going to outline now.

There's a group of patients, who are actually the most common patients that we see, who have what we refer to as low-risk disease. This would be solitary non-invasive cancer that's less than three centimeters, that's low grade. And the standard of care for treatment is to have the tumor removed through a cystoscope. That's generally a procedure that's done in the operating room, and then oftentimes we'll give a single dose of chemotherapy, not BCG right after the procedure. That's really all that they need. The guidelines don't support using BCG in this setting. I think it's safe to say that most urologists probably don't use it in this setting.

American Urologic Association Guidelines for managing BCG shortages (1 of 3)

- BCG should not be used for patients with low-risk disease.
- Intravesical chemotherapy should be used as the first-line option for patients with intermediate-risk NMIBC. Patients with recurrent/multifocal low-grade Ta lesions who require intravesical therapy should receive intravesical chemotherapy such as mitomycin, gemcitabine, epirubicin or docetaxel instead of BCG.
- If BCG would be administered as second-line therapy for patients with intermediate-risk NMIBC, an alternative intravesical chemotherapy should be used rather than BCG in the setting of this BCG shortage.



The next thing is that, the next group of patients is called intermediate-risk disease. They still have non-invasive low grade disease, but now they've recurred. In other words, this is their second or more tumor events and they may have multiple tumors in the bladder at the same time. There is a standard of care for those patients to be treated with either chemotherapy instilled into the bladder. We use a variety of different drugs. They're listed here on the slides instead of BCG.

But BCG is also considered a standard of care, and what we've recommended because of this shortage that BCG no longer be used in this setting. Patients will not sacrifice, in my opinion, any reduction in efficacy because we have a lot of experience with these chemotherapy drugs and particularly mitomycin and in this particular disease state of intermediate-risk disease, they're very effective. I think that if urologists curtail the use of BCG for this group of patients, then that'll go a long way towards alleviating the demand.

Seth Lerner: BCG should be held as a backup treatment in case chemotherapy doesn't work in this setting. And we now also can use two different chemotherapy agents in the same treatment session. Many people are using a combination for instance, of gemcitabine and docetaxel. Usually we're using that for our higher risk patients, but it's also an option for patients with intermediate-risk disease that's recurred after single agent chemotherapy. BCG is very effective, and we just want to hold it for those patients who have failed conventional intravesical therapy.

The challenge for patients who present with high-risk disease, so that's any patient with a high grade cancer, especially T1, which is an early invasive cancer, but not into the muscle. Carcinoma in situ is a high grade cancer that's just in the lining of the bladder. Those patients should be prioritized for using full strength BCG because that clearly is the standard of care. If BCG is not available, these patients and other high-risk patients can be given a reduced dose of BCG, and many of us will combine a reduced dose of BCG with another immunotherapy drug, called Interferon. The combination of BCG and Interferon may be good for patients recur with a high grade cancer after induction or six weeks of BCG or after a period of time where they've been treated with BCG and then recur with a new tumor. The benefit there is that you can reduce the dose of BCG and therefore, what many of us do is we can take a vial of BCG and split it between two or three patients in order to maximize the benefit.

American Urologic Association Guidelines for managing BCG shortages (2 of 3)

- For patients with high-risk NMIBC, high-grade T1 and CIS patients receiving induction therapy, they should be prioritized for use of full-strength BCG. If not available, these patients and other high-risk patients should be given a reduced 1/2 to 1/3 dose, if feasible.
- If supply exists for maintenance therapy for patients with NMIBC, every attempt should be made to use 1/3 dose BCG and limit dose to one year.
- In the event of BCG supply shortage, maintenance therapy should not be given and BCG-naïve patients with high-risk disease should be prioritized for induction BCG.



Seth Lerner: Then if the patient does respond and gets induction or this six weeks of BCG, then instead of using full dose BCG for maintenance, then we can use a reduced dose and treat at least up to one year. If BCG really is tight, if the supply is tight, then we have to prioritize patients who need to be treated with that initial six-week course of BCG. That's what we call induction. There is some other situations where we have to be a bit creative, and they're often situations where either BCG has been tried, it's no longer effective. The terminology for those patients is BCG unresponsive disease, and that's typically patients who recur with a high grade cancer after receiving induction plus one round of maintenance. BCG is not appropriate therapy after that, and we've listed in the slide here a number of different options. I've mentioned already, the combination of gemcitabine/docetaxel. We've also used gemcitabine/mitomycin, and we can use that for induction and maintenance in the patient who no longer is felt to be a good candidate for BCG.

Seth Lerner: And then there's a group of patients where BCG is no longer effective, and we're starting to encounter a risk of progression to a worse cancer or muscle invasive cancer, and there's clear indications for some of those patients that removing the bladder, or radical cystectomy, if they're considered to be well enough to undergo the operation, that can be curative. That really doesn't change. We'd like to think that that doesn't change in this BCG shortage. It wouldn't be ideal if a patient simply because of a shortage of BCG, their only alternative is to remove their bladder. Fortunately, we have a lot of experience with these other chemotherapy drugs that I think most of us are comfortable giving that a try before moving on to radical surgery.

American Urologic Association Guidelines for managing BCG shortages (2 of 2)

- If BCG is not available, a preferable alternative to BCG is mitomycin (induction and monthly maintenance up to one year). Other options such as gemcitabine, epirubicin, docetaxel, valrubicin or sequential gemcitabine/docetaxel or gemcitabine/mitomycin may also be considered with an induction and possible maintenance regimen.
- Patients with high-risk features (i.e., high-grade T1 with additional risk factors such as concomitant carcinoma in situ, lymphovascular invasion, prostatic urethral involvement or variant histology) who are not willing to take any potential oncologic risks with alternative intravesical agents, should be offered initial radical cystectomy, if they are surgical candidates.



Rick Bangs: We just wanted to offer up some trials that would be appropriate for patients to consider in the BCG-naïve stage. In other words, they have not had BCG so these are three that are currently available and can be seen on the BCAN dashboard or on clinicaltrials.gov. Trials do change over time, so these are three that are relevant today, but there may be others in the future.

Seth Lerner: Since we have the principal investigator of the PRIME trial ... Rob, do you want to give a quick overview, just to give an update on the BCG supply for that trial?

Robert Svatek: Yes, so that's the first one listed there is PRIME (S1602), which is available to many sites in many states. The trial involves randomization of patients to either TICE BCG or Tokyo strain. There's a third arm that can get Tokyo strain with an extra vaccine given intradermal. There's more details that are available there at clinicaltrials.gov or on the BCAN site. We have been in contact with Merck, the supplier of TICE, who has graciously been able to assure a provision of TICE BCG for patients on trial for both that first trial, as well as their KEYNOTE trial. That, at least for patients on trial, they'll have a steady supply for the induction and maintenance course.

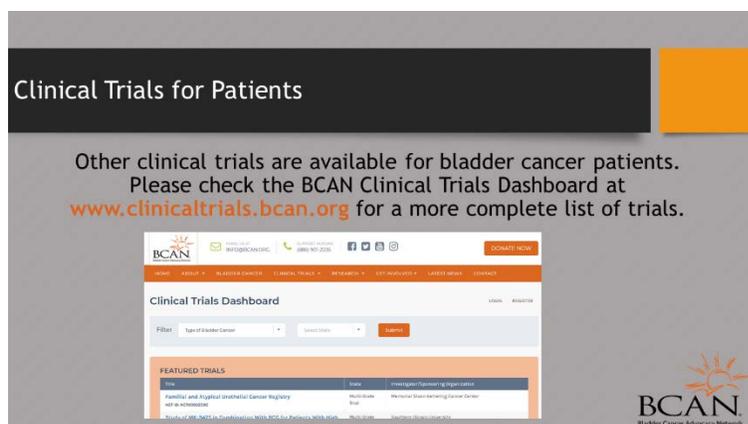
Clinical Trials for BCG-naïve patients

- PRIME (S1602): Different Strains of BCG With or Without Vaccine in High Grade Non- Muscle Invasive Bladder Cancer (clinicaltrials.gov Identifier: NCT03091660)
- KEYNOTE-676 Efficacy and Safety of Pembrolizumab (MK-3475) in Combination With BCG in High-Risk Non-Muscle Invasive Bladder Cancer (clinicaltrials.gov Identifier: NCT03711032)
- Phase 1/2 Study of ABI-009 in Nonmuscle Invasive Bladder Cancer (clinicaltrials.gov Identifier: NCT02009332)



I do want to point out that this is not comprehensive, does not include all potential trials out there that are available. There may be trials that are unique to your particular site that may be available that we're just not seeing in our reviews. You can talk to your local urologist about what trials they may have available there that may not be listed here.

Stephanie C: There are other clinical trials relating to bladder cancer specifically are available on our Clinical Trials Dashboard. If you visit clinicaltrials.bcan.org, you can get a more complete list of trials. It allows you to enter the diagnosis that you might have, and then you can select the state that you live in or where you could potentially engage in a clinical trial. And you're able to save those trials. You can establish an account, and you could email them directly to your healthcare providers if you were interested in getting their opinion on whether a clinical trial might be the right thing for you. BCAN only has bladder cancer clinical trials on this website, but it's the same trials that are listed on clinicaltrials.gov. We have a special feed that goes directly to us with all the open trials, the trials that are recruiting patients currently.



Stephanie C: Rick, would you want to talk a little bit about the patient perspective?

Rick Bangs: Sure. Let me start by saying BCG is very early immunotherapy. We don't normally think of bladder cancer, at least historically, we did not think of bladder cancer as being on the leading edge or the cutting edge. But in point of fact, this is before immunotherapy became popular in the last few years. An old treatment is not necessarily a bad treatment. That's

why we do clinical trials is we try to compare a new treatment alternative with an existing treatment alternative. Something that's already available is not necessarily worse than something that's new. The second point here is that BCG is effective for many patients, and it has acceptable side effects. But it is not effective for anyone and that leaves open the possibility for better coverage and more effectiveness and some of the clinical trials that we have talked about tonight. There's some inconsistency in the administration of maintenance BCG. There are some

BCG: The Patient Perspective

- Very early immunotherapy (late 1980's)
- Effective for many, with acceptable side effects
- Even today, mechanism of action is not well understood
- Relatively low cost, especially compared to new alternatives being studied
- Biologic that is challenging to consistently produce
- Third shortage in about seven years
- Three clinical trials relevant to patients who have not started BCG treatment



guidelines that are published, but there may be some inconsistency in how people interpret the use of maintenance BCG. The side effects are generally acceptable, but there are some patients who would have some difficulty.

Even today, almost 30 years later, the mechanism of action is not well understood. One of the things that's being done with the trial that Dr. Svatek talked about, the S1602 trial, is to better understand how BCG is actually working so that we can better understand how to treat bladder cancer.

It is relatively low cost and that is always an important factor for patients, especially compared to some of the new alternatives that are being studied. Things like immunotherapies tend to have fairly significant cost and BCG is, on the relative scale of things, a low-cost treatment.

These new alternative treatments and low profitability are likely going to hinder the building of additional capacity by the BCG manufacturers.

Rick Bangs: The next point is that it's a biologic. You heard that it grows on potatoes. It's challenging to consistently produce. You don't get 100% every time. As I understand it, you don't know until the end of the growth cycle if you will, that the batch is not going to be good so that makes it additionally challenging to produce. This is our third shortage in about seven years. I can tell you from looking at the BCAN Inspire site that survivors are angry, frustrated and incredulous that we are where we are. It's I think relatively unclear to us why we have a shortage, although we do know that there is some reported increase in demand, and we're looking for some accountability for supply.

Patients can be confused about their treatment plan and unwilling to accept lesser alternatives, and so we walk through what those alternatives are. Dr. Lerner gave you an assessment of the alternatives and how successful they might be relative to BCG. But as patients, we're a little bit concerned on that. Many patients are not complacent and are willing to work on fixing the short and long term problem, and there's been some discussion tonight about how to do that. We'll have a little more discussion in the next few minutes on that.

The maintenance guidelines proposed during the shortage are concerning. I understand that there may be some billing challenges with partial doses, although I understood that those were being addressed, and hopefully we've reached some conclusion on that.

Finally, there are at least three clinical trials that patients may want to consider. There may be additional trials coming up, so by all means talk to your doctor and find out what makes sense for your situation. These trials are testing alternatives alone or in combination with BCG. To my knowledge, there are no trials for substituting an alternative treatment after you've started BCG. I think in a perfect world we would have that, but the challenge is that alternative treatments have to prove themselves in untreated patients first. We don't have a trial available to my knowledge that allows you to have started BCG and then switch to certainly another strain or an alternative treatment. But by all means, talk to your doctor about that possibility.

Clinical trials are not accessible to everyone due to the distance from the location where you would get the clinical trial. Work with your doctor, find out what makes sense for you in terms of where you live or where you could go for treatment, whether it's a member of your family or a friend that you could stay with during treatment. They may be a little more accessible if you open up to those possibilities. But they are not universally available. You cannot go to just any location and get a clinical trial.

Stephanie C: We really wanted to just give you some other suggestions too about how you can navigate for more options. This is clearly a big concern. This is a global problem. We were notified by Merck at the beginning of the year that they anticipated this shortage and they had ramped up production. And yet, they're still unable to meet the demand for the BCG. This is a global concern and so that was one of the questions that has already come in.

Stephanie C: Definitely consider a BCG alternative clinical trial as part of your treatment. Talk to your doctor about that. If you know other bladder cancer patients, you could also pass that along to them if they weren't able to be on this call. Please watch BCAN.org for more communications and more ideas. We have the BCG shortage at the top of our website, and we're trying very hard to keep that as updated as we can.

You can also help us to advocate for more funding in the research space. If we can get more of these drugs through the clinical trials and into the approval process, and we will definitely be helping to spearhead that however we can as an organization through the FDA approval process, we will definitely do that. But definitely looking at more options for research in this area to find alternative treatments or approval of different strains is definitely going to be something that we hope will help to shorten this current shortage.

How You Can Advocate for More Options

- Consider a BCG alternative clinical trial before treatment.
- Suggest that other patients consider trials as you connect with them.
- Watch future BCAN communications for ideas
- Advocate for more funding in the research space (Government, Pharmaceutical companies)

