



# INTERNATIONAL BLADDER CANCER GROUP (IBCG)

## **BCG: What to do when there is a Shortage**

**A brief Q&A for patients by the International Bladder Cancer Group (IBCG) -** Ashish M. Kamat, Roger Buckley, J. Alfred Witjes, Mark Soloway, Donald L. Lamm, Raj Persad, Andreas Bohle, Joan Palou, Marc Colombel, Prem Kumar, Maurizio Brausi

### **Introduction**

Intravesical therapy may be an important component of the management of bladder cancer (BC). The delivery of anti cancer medication directly into the bladder with a catheter placed into the bladder through the urethra has been a part of bladder cancer (BC) management for many decades. All patients with BC have an initial transurethral resection (TUR BT) which is designed to remove all of the tumor, when possible. The tumor tissue is then submitted to the pathologist for diagnosis. The pathology report states the tumor grade as well as the presence or absence of invasion into the muscular layer of the bladder. The urologist will review this information and along with his/her understanding of the appearance of the bladder cancer, as well as their impression of whether all of the tumor has been removed to decide about the treatment strategy.

If the pathology report from the initial TUR BT indicated a high grade tumor confined to the surface (high grade Ta) or a high grade tumor which invaded only into the lamina propria (high grade T1) the urologist will likely suggest a course of Bacille Calmette-Guérin (BCG) after trying to ensure that all of the bladder cancer appears to have been removed by the TUR BT.

If the pathology report indicates that the cancer is low grade and is confined to the surface (low grade Ta) the decision might be to monitor the patient with periodic cystoscopy with or without additional intravesical therapy. If he/she suggests intravesical therapy the choice would be intravesical chemotherapy. If these low risk tumors continue to develop despite the initial approach, BCG is one of the recommended agents for intravesical therapy.

### **How is BCG made?**

BCG is made in specialized pharmaceutical factories that are able to grow the bacteria in a sterile environment. The life cycle to produce BCG is about 3-4 months long. The BCG is grown with potatoes in a specialized environment. Just like any agricultural crop the yield of that particular BCG lot can vary from time to time. This is also the reason why production cannot be suddenly increased to meet a larger demand for the product. In addition, when any of the ingredients or supplier of ingredients used in the cultivation of BCG are changed, which happens periodically, approval must be obtained from the regulatory agencies used for each country. This process, while meant to protect patients, appears to more often than not to restrict the availability of BCG, and is one of the reasons the Connaught strain of BCG is no longer available.

Once the BCG has been produced it is then passed through quality control measures, freeze dried in small vials, packed and then distributed around the world. The distribution involves a cold chain process which means that these BCG vials have to be maintained at a certain cold temperature throughout the entire journey of trucks, planes and distribution vehicles to the hospital or clinic.



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### Who makes BCG?

BCG is produced in specialized factories around the world. Until recently, the 2 main suppliers for the North American and European market were Sanofi Pasteur in Toronto, Canada and Merck in the USA. BCG is also produced in Germany by MEDAC. There is only a single factory for each producer. There are a number of other BCG strains that are produced in other countries including Japan, India and Russia. These other strains are not currently approved for use in the US or Canada.

### If there is a shortage of BCG what are my options?

Unfortunately, we are currently facing a shortage of BCG which will be similar to a previous shortage from 2012-2016. There are several suggestions to deal with this shortage.

For high risk bladder cancer patients 1/3 dose of BCG should be considered for your induction and maintenance therapy. This will allow that vial of BCG to be utilized for 3 patients. Maintenance BCG can also be shortened to one year rather than the 3 years suggested for some patients – mainly those with lower risk tumors. Both measures have shown to result in a somewhat higher risk of recurrence, but not disease progression, so in that sense these adaptations seem to be safe alternatives when the full dose is not available.

For intermediate risk patients (with low grade disease) intravesical chemotherapy may be used as a first line option instead of BCG immunotherapy. If BCG is needed as second line therapy for intermediate risk patients then 1/3 dose should be utilized. Maintenance BCG therapy can be omitted for intermediate risk patients.

BCG immunotherapy should not be utilized for low risk patients.

We would also recommend you contact your urologist about being referred to a site participating in the SWOG study SW1602, which is comparing Merck's BCG (Tice) to the Japanese BCG (Tokyo-172 Strain). It is only through studies like this that the FDA will allow other BCG strains to be approved in the US which would be required before we can get access to them.

### Is a reduced dose of BCG as effective as a full dose?

There is global consensus that it is acceptable to use 1/3 dose of BCG instead of a full dose and that duration of treatment is more important than size of the dose used. Most initial studies in the bladder cancer population were done utilizing a full dose of BCG. However, there was a very large study involving over 1400 patients that suggested a reduced dose of BCG could produce an acceptable immune response in the patient. As mentioned before, a reduced dose results in a somewhat higher risk of recurrence, but not progression of the bladder cancer, so in that sense 1/3 dose is considered safe. For some select high risk patients your physician might choose a full dose of BCG for your induction therapy. It is reassuring that in the large EORTC study (Oddens et al, Eur Urol. 2013 Mar;63(3):462-72) a 1/3 dose BCG did not significantly increase tumor recurrence when



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compared to full dose given for the same time period. One third dose for 3 years was numerically but not significantly better than full dose for one year.

### **If BCG is not available at all what are my options?**

Standard intravesical chemotherapy with a number of different agents including mitomycin, doxorubicin, epirubicin or other chemotherapies including gemcitabine and docetaxel can be offered if BCG is not available. These typically would involve an induction and maintenance regimen up to 1 year. There are some variations of intravesical chemotherapy such as electromotive mitomycin (EMDA-MMC) or hyperthermia that may be available in some centers but not in the US at this time.

If patients have high risk or very high risk disease an upfront radical cystectomy to remove the bladder is always an option. This may involve patients that have high risk pathological variants, carcinoma in situ or patients who would not be willing to take a potential oncological risk with alternative intravesical agents.

### **Are there any ongoing trials involving new therapies?**

There is an ongoing European study that is evaluating the reduction of the number of instillations of BCG (NIMBUS). There is significant research in the use of new immunotherapeutic agents. These have been utilized for a number of different cancers and are currently being explored for muscle invasive bladder cancer. Ongoing trials are studying the use of these agents in the NMIBC patient population, although most of these trials are specifically in patients that did have a response to their initial adequate BCG therapy.



*Leading the way to awareness and a cure*

The Bladder Cancer Advocacy Network would like to thank the members of the International Bladder Cancer Group for this important update about the 2019 BCG shortage. For additional information, please visit [www.BCAN.org](http://www.BCAN.org) (02 | 12 | 19)