



# High dose Bacillus Calmette-Guerin (BCG) for urothelial carcinoma is trickier than expected

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Comment on: Shah G, Zhang G, Chen F, *et al.* The Dose-Response Relationship of bacillus Calmette-Guérin and Urothelial Carcinoma Cell Biology. *J Urol* 2016;195:1903-10.

Submitted Dec 15, 2016. Accepted for publication Jan 11, 2017.

doi: 10.21037/tcr.2017.02.04

View this article at: <http://dx.doi.org/10.21037/tcr.2017.02.04>

Intravesical instillation of Bacillus Calmette-Guerin (BCG) is the first line adjuvant therapy to transurethral resection of bladder tumor (TURBT) for patients with intermediate- and high-risk non-muscle invasive bladder cancer (NMIBC) lesions (1). Its effectiveness, however, comes at a cost of complications, with up to 91% of patients developing some type of irritative local symptoms (1). Additionally, about 10–20% of responders and 66% of non-responders eventually progress to muscle-invasive disease, leaving them with an invasive option of cystoprostatectomy (2).

As mentioned in the current paper, researchers have been attempting to find ways to reduce morbidity associated with intravesical BCG therapy without compromising its efficacy. To that effect, trials have shown that a third of the standard dose has similar efficacy in intermediate-risk superficial tumors with improved side effect profile. However, what can improve response rates to the above therapy, especially in BCG unresponsive patients, remains unknown. This paper takes a key step in this direction by evaluating the effects of BCG dose escalation in both *in vitro* and *in vivo* settings. By using two different TCC cell lines, T24 and 253J, they have shown that BCG dose escalation from the standard cell-to-BCG ratio of 1:50 to up to 1:500 led to dose-associated response at the cellular level. This is manifested in improved BCG attachment and internalization in cells, increased activation of several signaling pathways, increased RNA levels of key immune response genes, and increased cell death. Additionally, the *in vivo* study involving an orthotopic murine model of

bladder cancer showed improved response to escalating intravesical BCG dose.

While the reported findings are encouraging and warrant further research in BCG dose escalation, it is noteworthy that the two cell lines behaved differently at the same concentrations of BCG. For instance, CEBP intracellular signaling pathway had its peak activity at 1:200 and 1:500 for T24 cells and 253J cells, respectively. Similarly, only 4 of 7 BCG related genes were activated in T24 compared to 7 of 7 genes in 253J cell line. From these results, it is clear that there are fundamental biological differences between TCC cell lines that we do not, yet, fully understand. This also holds true for actual bladder cancers, as reflected in some lesions being more BCG susceptible than others.

In addition to the highlighted molecular differences, the *in vivo* data must also be cautiously evaluated. With the short follow-up after intravesical BCG instillation and no reported data on changes in mice weight after treatment, it is difficult to discern how well these mice tolerated the escalation in BCG dose. Given that a large proportion of patients receiving standard BCG dose experience significant, yet tolerable, side effects, it will be important that any escalation in BCG dose does not achieve its efficacy at the expense of increased morbidity. Hence, a fine line between efficacy and morbidity will have to be maintained.

In conclusion, we are desperate for better treatment options for patients who fail intravesical BCG therapy for bladder cancer. This could be due to the fact that our current standard dose is insufficient, as proposed by this

current paper, or that some patients have biological factors that deem them BCG unresponsive. While we wait for better treatments to be developed, it may be worthwhile to evaluate the escalation in the BCG dose in such patients. After all, the clock is ticking on them!

### Acknowledgments

*Funding:* None.

### Footnote

*Provenance and Peer Review:* This article was commissioned and reviewed by the Section Editor Peng Zhang (Department of Urology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China).

*Conflicts of Interest:* Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2017.02.04>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related

**Cite this article as:** Siddiqui MR, Agarwal PK. High dose Bacillus Calmette-Guerin (BCG) for urothelial carcinoma is trickier than expected. *Transl Cancer Res* 2017;6(Suppl 1):S31-S32. doi: 10.21037/tcr.2017.02.04

to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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