Perspective

Is dose-dependent response to bacillus Calmette-Guérin treatment in urothelial carcinoma?

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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.

Abstract: Bacillus Calmette-Guérin (BCG) intravesical instillation therapy has been established as a standard of care treatment for high-risk non-muscle invasive urothelial carcinoma (NMIUC). To date, many clinical have demonstrated a direct antitumor activity, prevention of tumor recurrence, reductions in tumor progression and, consequently, tumor specific mortality and improvement in overall survival. Nevertheless, the local adverse events arising from BCG intravesical account for about one-third of treatment discontinuations. Strategies to minimize the side effects are needed.

Keywords: Non-muscle invasive (NMI); urothelial carcinoma (UC); toxicity; Bacillus Calmette-Guérin (BCG); standard doses (SD); high doses

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Bladder cancer (BC) is a major global health challenge with 430,000 new cases and nearly 165,000 deaths during 2012. In 2012, estimated BC incidence and mortality in Europe were 151,297 and 52,411 cases, respectively (1). Urothelial carcinoma (UC) is the most common histologic subtype of BC, and represents nearly 90% of all cases. Approximately 75% of patients with BC present with a disease confined to the mucosa (stage Ta, CIS) or submucosa (stage T1) (2). The high grade tumors have been recognized as an important prognostic factor with regard to the potential for disease recurrence and progression. In patients with high-risk non-muscle invasive UC (NMIUC) the transurethral resection with intravesical Bacillus Calmette-Guérin (BCG) is the standard treatment (3).

Immunotherapy with BCG results in a massive local immune response characterized by induced expression of cytokines in the urine and in bladder tissue, and by an influx of granulocytes into the bladder wall. A larger set of cytokines, including TNF-α, GM-CS, IFN-γ and several IL has been detected in the urine of patients treated with intravesical BCG. These cytokines are involved in the initiation and maintenance of inflammatory process (4).

Martínez-Piñeiro *et al*. studied the relationship between dose reduction and efficacy of intravesical BCG, which compared the standard dose (SD) of 81 mg of BCG with a reduced dose of 27 mg for the treatment in patients with NMIUC. Reduced dose had similar results for recurrence and progression but with significantly less toxicity (5). In another study Martínez-Piñeiro *et al*. compared if a third of the dose of intravesical BCG has the same efficacy than SD for decreasing the risk of recurrence and progression. The results suggest that a 3-fold decreased dose of intravesical BCG is as effective as the SD (6).

On the other hand, Shah *et al*. reported that higher dose of BCG showed a better antitumor effect in two human UC cell lines than a SD. The authors suggest that there is an optimal dose of BCG measured by a cellular response to BCG and there is a rational for perform a dose escalation for improve response rates (7).

The authors of this paper use two human cell lines derived from UC at different concentrations of *in vitro* BCG from 1:5 to 1:500 confirming the adhesion and

internalization of BCG in most of the different groups of cell lines. They demonstrated that UC cells exposure to BCG generated an activation of NFκB and this activation was correlated with BCG dose. The effect of the BCG dose on UC cells and gene expression was evaluated by quantitative RT-PCR. Only in the cell line 253J there was a relationship between BCG dose and gene expression (iNOS, CD45, IL6, CXCL1, CXCL3, IL8 and CCL20) in response to BCG.

Intravesical BCG is a treatment that causes serious side effects in many patients. The largest published study with BCG including 1,316 reported 62.8% of local side effects and 30.6% had some form of systemic side effects (8).

There are several strategies to diminish the toxicity. One of them is lowering the BCG (6). This approach diminishes the frequency of side effects but certainly not the severity of adverse events, which are the reason for stopping the treatment with BCG. Another strategy is the preventive systemic administration of isoniazid (INH). EORTC study 30911 addressed this clinical question. However, INH provoked transient liver toxicity in several patients. So, the use of prophylactic INH is not recommended (9). The last approach is the preventive symptomatic treatment with anticholinergic drug as such oxybutynin. The results were disappointing as the significantly worse outcome was in the oxybutynin arm when was compared with placebo arm (10).

The next question is how we can go move forward to increase the doses of BGC in the clinical setting? The authors propose further research will be conducted in a phase I trial in population of patients refractory to SD.

In contrast to the general belief that side effects increase over time, frequency was similar in the induction treatment and the maintenance therapy. Most treatment discontinuations for severe side effects occurred in the first year, so severe adverse events can already appear at the first instillation, this observation reveals that side effects are not dependent on the number of instillations but upon the host. Recently, Serretta *et al*. reported that almost 60% of patients interrupted the treatment due to persistent toxicity with SD of BCG (11).

At the moment data demonstrated that none of the earlier advocated methods to prevent BCG toxicity are effective. On the other hand, severe complication will occur if the patients are treated with higher doses of BCG.

Therefore, since the study lacks for decrease the toxicity of BCG and inacceptable toxicity induced by higher doses of BGC any dosing strategy that increases the SD of BCG will produce an absolute intolerance to intravesical BCG.

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Footnote

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References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86.
2. Chalasani V, Chin JL, Izawa JI. Histologic variants of urothelial bladder cancer and nonurothelial histology in bladder cancer. Can Urol Assoc J 2009;3:S193-8.
3. Babjuk M, Burger M, Zigeuner R, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. Eur Urol 2013;64:639-53.
4. Fuge O, Vasdev N, Allchorne P, et al. Immunotherapy for bladder cancer. Res Rep Urol 2015;7:65-79.
5. Martínez-Piñeiro JA, Flores N, Isorna S, et al. Long-term follow-up of a randomized prospective trial comparing a standard 81 mg dose of intravesical bacille Calmette-

Guérin with a reduced dose of 27 mg in superficial bladder cancer. BJU Int 2002;89:671-80.
6. Martínez-Piñeiro JA, Martínez-Piñeiro L, Solsona E, et al. Has a 3-fold decreased dose of bacillus Calmette-Guerin the same efficacy against recurrences and progression of T1G3 and Tis bladder tumors than the standard dose? Results of a prospective randomized trial. J Urol 2005;174:1242-7.
7. 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.
8. Brausi M, Oddens J, Sylvester R, et al. Side effects of Bacillus Calmette-Guérin (BCG) in the treatment of intermediate- and high-risk Ta, T1 papillary carcinoma of the bladder: results of the EORTC genito-urinary cancers group randomised phase 3 study comparing one-third dose with full dose and 1 year with 3 years of maintenance BCG. Eur Urol 2014;65:69-76.
9. Vegt PD, van der Meijden AP, Sylvester R, et al. Does isoniazid reduce side effects of intravesical bacillus Calmette-Guerin therapy in superficial bladder cancer? Interim results of European Organization for Research and Treatment of Cancer Protocol 30911. J Urol 1997;157:1246-9.
10. Johnson MH, Nepple KG, Peck V, et al. Randomized controlled trial of oxybutynin extended release versus placebo for urinary symptoms during intravesical Bacillus Calmette-Guérin treatment. J Urol 2013;189:1268-74.
11. Serretta V, Scalici Gesolfo C, Alonge V, et al. Does the Compliance to Intravesical BCG Differ between Common Clinical Practice and International Multicentric Trials? Urol Int 2016;96:20-4.

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