Editorial Commentary

Enhanced power bacillus Calmette-Guérin—possibly too much of a good thing

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Intravesical bacillus Calmette-Guérin (BCG) immunotherapy is the standard adjuvant treatment in patients with intermediate- and high-risk non-muscle invasive bladder cancer (NMIBC) after transurethral resection of the bladder tumour (TURB). It was widely proven, that this therapy reduces the risk of tumour recurrence and, what is more important, the risk of cancer progression. However, despite decades of BCG usage, precise mechanism, optimal schedule, dosage and various other details remain unknown. Furthermore, some patients do not respond well to the therapy, while others develop side effects. Finally, we have to face the BCG shortage because of production and logistics issues (1). All these factors motivate and promote the search for BCG alternatives or classic BCG ameliorations.

In the paper by Rodriguez *et al.* published recently in the Frontiers in Immunology Journal authors analyse biological and immunological potential of recombinant BCG Moreau strain (2). Authors should be praised for preparing methodologically sound study assessing the influence of bacilli on many different areas of immunological response. The provided data proves that rBCG-S1PT strain enhances immune activation when compared to wild type BCG in terms of cytokine production and tumour cytotoxicity.

Yet, there is the other side of the coin. It should be emphasized that alike BCG effectiveness, BCG toxicity is generated by immunological properties of bacilli. Those two phenomena are somehow link and therefore, some authors advocate the "no pain-no gain" hypothesis which state that the higher the toxicity the better are the oncological results. However, the pathogenesis of adverse reactions following intravesical BCG instillation has not been fully explained. Having all that in mind, one should assume, that enhancing the immune-inducing properties of the intravesical instillation will probably increase the treatment toxicity. As we know from cohort studies, almost all patients experience some side effects, whereas they are graded as severe in as many as 30% of cases. Because of that, in many cases, side effects of BCG therapy impose dose reduction or force treatment cessation (3). Therefore, it is possible, that additional BCG strengthening will significantly limit its application options.

As authors highlight in their paper, the *in vitro* immunological response to the intravesical BCG therapy varies significantly between individuals. This is also obvious in clinical setting. We all know that despite implementation of "proper" BCG schedule, in some patients the oncological response is not optimal and the disease progresses. This raises the necessity to find the definitive causes of variety phenomenon, or at least precise predictive factors of therapy outcome. Unfortunately, despite intensive search, all analysed factors have proved limited efficacy (at best). From studies on muscle invasive bladder cancer, it seems, that the most promising future prediction models will be based on genomic profile and genomic biomarkers, e.g.,

mutations in DNA damage and repair genes (4). As it was recently shown, that about 30% of high-grade NMIBCs harbour these mutations (5).

The next interesting issue raised by the authors concerns influence of previous BCG immunisation. In the available literature we can find various papers analysing this problem, yet, the result is conflicting and the ultimate answer is unknown. Authors of this study show that there were differences in cytokines levels between vaccinated and non-vaccinated patients. Yet, the conclusion should be drawn with caution as the examined population was very small and as vaccination is not the sole origin of mycobacterial immunization.

Finally, recombination of BCG bacilli does not respond to the problem of BCG shortage, which nowadays seems to be the most significant BCG-related issue in Europe. Researchers focus more and more on establishing alternative regimens instead of improving BCG. Even the most effective BCG recombination would remain useless if BCG would not be available.

Last but not least, the in vitro results do not always translate directly into clinics, so we need to cross our fingers for upcoming clinical trial on rBCG-S1PT and hold our optimism until we see their outcomes.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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