Editorial

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Future therapeutic perspectives of BCG therapy for bladder cancer: an evolving horizon

https://doi.org/10.1515/jbcpp-2025-0106

Keywords: non-muscle-invasive bladder cancer; Bacillus Calmette-Guèrin (BCG); biomarkers; intravescical treatment; personalized medicine

Introduction

Non-muscle-invasive bladder cancer (NMIBC) represents one of the most frequent and challenging urological malignancies due to its high recurrence rate and potential for progression. For over four decades, intravesical treatment with Bacillus Calmette-Guérin (BCG) has been the cornerstone of therapeutic strategies in high-risk patients. However, the current clinical landscape is undergoing a profound transformation, driven by various factors such as the increasing global shortage of the vaccine, the emergence of refractory cases, and a growing understanding of the immunological mechanisms underlying the antitumor response. In this context, there is a pressing need to redefine the role of BCG, identifying alternative or complementary approaches that can overcome its limitations without compromising its historically proven efficacy.

Contribution of the authors: Michele Musone is both the first and senior author of this editorial. He conceived the topic, performed the literature analysis, drafted the manuscript, and supervised its development and finalization. Stefano Chianese, Ciro Chervino, and Tiziana Rotunno contributed to the critical revision of the manuscript for important intellectual content and approved the final version for submission. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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BCG efficacy and toxicity: a balance to be renegotiated

BCG has demonstrated, over decades of clinical practice, significant efficacy in reducing recurrences and disease progression. In high-risk patients, it remains the first-line option for intravesical treatment, showing better results than intravesical chemotherapy [1]. However, this efficacy must be weighed against a tolerability profile that, in some cases, limits its use or leads to early discontinuation. Many patients experience significant irritative symptoms, hematuria, or chemical cystitis that impair quality of life and adherence to treatment. Although severe systemic adverse events, such as disseminated BCG infection, are rare, their potential severity warrants careful consideration. Moreover, not all patients respond adequately to treatment: it is estimated that about 40 % may experience recurrence despite full exposure, and around 15 % may progress to muscle-invasive disease [2]. This highlights the need to personalize the therapeutic strategy, assessing early on the likelihood of response and the indication for alternative treatments. The NIMBUS trial, which evaluated the possibility of reducing the frequency of instillations, demonstrated that insufficient immune stimulation compromises clinical efficacy, reaffirming the importance of complete regimens, though balanced with regard to toxicity [3]. In addition to clinical tolerability, BCG management today also faces logistical and manufacturing challenges. The global shortage of the vaccine has led to usage rationalization and stricter patient selection. Furthermore, the lack of reliable biomarkers to predict response represents a major limitation in optimizing treatment, making BCG indication still largely empirical.

New therapeutic scenarios: synergies, substitutions, and innovations

Given these challenges, scientific research is increasingly exploring alternative therapeutic strategies capable of overcoming the limitations of conventional BCG therapy.

One of the most promising directions involves combining BCG with immune checkpoint inhibitors such as pembrolizumab or atezolizumab. The goal is to enhance the local immune response induced by BCG by reinforcing it with a systemic effect. Preliminary data suggest a benefit in disease control among BCG-refractory patients, paving the way for conservative options to delay or avoid radical cystectomy [4]. At the same time, the FDA approval of nadofaragene firadenovec marked a significant step forward. This gene therapy, based on a recombinant adenovirus capable of delivering IFN-α2b directly to the bladder mucosa, has shown sustained response rates and a favorable tolerability profile in clinical trials, making it a valid option for patients unresponsive to BCG [5]. Other similar vector-based platforms are currently under development, aiming to deliver immunoactive molecules in situ – such as cytokines or toll-like receptor agonists – capable of inducing local activation of antitumor immunity [6]. Another area of innovation involves the development of alternative bacterial strains to BCG, designed to possess greater immunogenicity and lower virulence. These "next-generation BCGs," potentially more standardized in manufacturing processes, could provide effective solutions to both logistical and tolerability issues. The interest in a systemic approach to immune modulation – so far reserved for advanced tumors – is gradually extending to NMIBC as well [7]. Preclinical studies and early-phase trials are exploring the potential of systemic immune "priming" before BCG instillation, or the use of adjuvant strategies after endoscopic resection in very high-risk patients. If validated, such approaches could completely redefine NMIBC management, bringing it closer to the therapeutic paradigms used in muscle-invasive cancers [8].

Toward personalized medicine: biomarkers and new clinical endpoints

One of the main obstacles to optimizing BCG therapy is the lack of reliable predictive biomarkers. Current efforts focus on identifying immune gene signatures, analyzing tumor PD-L1 expression, and evaluating urinary cytokine panels [9]. Additionally, the use of circulating tumor DNA (ctDNA) or microRNAs may offer a non-invasive method to monitor early therapeutic response and guide potential treatment switching. If validated, these tools could allow more accurate patient selection and reduce overtreatment. Furthermore, the definition of clinical trial endpoints requires updating. Traditional indicators such as recurrence-free survival or progression need to be complemented by more specific parameters, such as time to radical cystectomy or sustained complete response rates in BCG-refractory patients, to better reflect the clinical impact of new therapeutic strategies [10].

Conclusions

BCG therapy for non-muscle-invasive bladder cancer remains a well-established platform, but it is far from immutable. Advances in immunological understanding and the development of new biological technologies are paving the way toward increasingly personalized and rational disease management. Moving beyond the traditional "one-size-fits-all" paradigm does not mean abandoning BCG, but rather integrating it into a multimodal model that leverages its strengths and addresses its weaknesses. In a constantly expanding therapeutic landscape, the future of NMIBC management lies in balancing efficacy, tolerability, and personalization, with the ultimate goal of providing patients with treatments that are more effective, sustainable, and tailored to their needs.

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