Editorial Commentary

Long-term efficacy of two sequential induction courses of Bacillus Calmette-Guérin in patients with high-risk non-muscle-invasive bladder cancer

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Current challenges and limitations of Bacillus Calmette-Guérin (BCG) therapy for non-muscle-invasive bladder cancer (NMIBC)

The management of high-risk NMIBC remains a significant clinical challenge owing to its high recurrence and progression rates. BCG therapy, particularly maintenance therapy, has long been the cornerstone of treatment for reducing the recurrence and progression rates in high-risk NMIBC (1,2). The superiority of maintenance BCG therapy over induction therapy alone has been well established, with studies showing significant reductions in recurrence and progression in patients with intermediate- and high-risk NMIBC (1). However, the optimal duration and schedule of BCG maintenance therapy remains the subject of ongoing research and debate (3).

Despite its efficacy, BCG therapy has several limitations. Firstly, a global shortage of BCG necessitates the exploration of alternative treatments and strategies (4). Additionally, BCG therapy often has significant adverse effects, which can limit its use, especially in older patients or those with comorbidities (5). These adverse effects can lead to discontinuation of treatment and suboptimal outcomes. Furthermore, the concept of BCG-unresponsive disease has emerged, highlighting a subset of patients who fail to achieve or maintain a disease-free state despite adequate BCG treatment (6). This has prompted an increased interest in identifying predictive biomarkers for the response to BCG and exploring novel treatment approaches for patients who are BCG-unresponsive.

Recent studies have focused on optimizing BCG therapy through combination therapies, alternative dosing schedules, and different strains, highlighting the current limitations of BCG therapy, and their potential impact on future clinical practice (7-13). As research continues, the goal remains to maximize therapeutic efficacy while minimizing side effects, ultimately enhancing the management of high-risk NMIBC.

Summary of the study design and methodology

The primary objective of this phase 2 clinical trial (14), conducted at the Memorial Sloan Kettering Cancer Center, was to evaluate the efficacy of two sequential induction courses of BCG in enhancing the therapeutic response among patients with NMIBC. Traditionally, BCG

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therapy consists of a 6-week induction course, followed by maintenance therapy comprising three-weekly treatments performed at 3, 6, 12, 18, 24, 30, and 36 months. However, this study explored the potential benefits of an additional 6-week induction course to address the ongoing BCG shortage and assessed its impact on long-term outcomes.

Between November 2015 and June 2018, 81 patients with high-risk NMIBC (high-grade Ta or T1 tumors, with or without carcinoma *in situ*) were prospectively assigned to receive two induction courses (12 intravesical instillations) of BCG without maintenance therapy. Among these, 77 patients had complete baseline data available for analysis. The median age at the first BCG treatment was 72 years [interquartile range (IQR): 64–77 years], and the cohort consisted predominantly of males (84%) rather than females (16%). Prior treatment history data indicated that 66% (n=51) of the participants had no previous exposure to BCG or mitomycin (MMC), whereas 18% (n=14) had prior BCG only, 12% (n=9) had prior MMC only, and 3.9% (n=3) had received both BCG and MMC. The disease stage prior to BCG treatment was distributed as follows: 32% (n=25) had pTa tumors, 39% (n=30) had pTis (CIS), and 29% (n=22) had pT1 tumors. Notably, 97% of patients had high-grade disease, meeting the inclusion criteria for high-risk NMIBC.

Of the initial 81 patients, 75 were deemed evaluable for long-term follow-up. Recurrence-free survival (RFS) and cancer-specific survival (CSS) were assessed over median follow-up periods of 4.4 and 4.9 years, respectively.

The results demonstrated a 5-year RFS rate of 69% and CSS rate of 97%, indicating that the two induction courses of BCG therapy provided sustained long-term efficacy. A subgroup analysis showed no significant differences in RFS by tumor stage, although detailed statistical comparisons across these subtypes are not a focus of the current report. Patients with prior BCG therapy demonstrated a slightly higher 5-year RFS [82%, 95% confidence interval (CI): 65–100%] compared to those without prior BCG therapy (65%, 95% CI: 53–80%), suggesting that previous immune priming may influence outcomes. However, the small sample size and single-center design limit the power of these comparisons, necessitating further multicenter studies for validation. The study also achieved a significant reduction in BCG use from 27 vials per patient to 12 vials. These findings indicate that an additional induction course may hypothetically enhance the immune response, as suggested by previous studies on immune modulation with additional BCG dosing, providing a viable alternative to standard BCG therapy with maintenance during periods of BCG shortage (15).

Strengths and limitations of the study

The primary strength of this study is its comprehensive 5-year follow-up period, which provides robust data on the long-term efficacy and safety of modified BCG therapy. The prospective study design with clear inclusion criteria and detailed follow-up procedures enhanced the reliability and validity of the findings. Additionally, the practical implications of this study are significant, particularly in the context of global BCG shortage. By demonstrating that two induction courses of BCG without maintenance can achieve significant oncological outcomes, this study offers a viable approach to reducing BCG usage.

A key comparison can be made with the EORTC study by Oddens *et al.*, which evaluated the efficacy of full-dose BCG with three years of maintenance (3). This study reported a 5-year RFS of 64.2% for high-risk NMIBC patients, providing a direct reference point for contextualizing the 5-year RFS rate of 69% identified by Katims *et al.* (14). Miyake *et al.* (16) investigated non-maintenance eight-dose induction BCG therapy and showed that, while its efficacy is lower than that of the six-dose induction plus maintenance BCG regimen, it still offers a potential alternative during BCG shortages. In their study, Miyake *et al.* reported a 2-year RFS rate of 83% for their overall cohort, reflecting their shorter follow-up period and different study design (16). Furthermore, Katims *et al.* (14) reported a CSS rate of 97%, highlighting the long-term survival benefits of the dual induction approach without maintenance, which is a crucial consideration in managing high-risk NMIBC. In contrast, the NIMBUS trial explored the potential of implementing a reduced frequency and dose of BCG instillations to address the BCG shortage (17). Unfortunately, this trial was halted early due to inferior oncologic outcomes among patients with high-risk disease. These findings underscore the necessity of maintaining the established SWOG regimen, particularly in high-risk NMIBC patients, to ensure optimal therapeutic efficacy.

This study had several limitations. Firstly, a relatively small sample size (77 patients) limited the generalizability of the findings. The single-center design may not fully capture the variability in patient responses and healthcare practices observed in other institutions, further affecting the generalizability of the results. Additionally, the lack of a control group precludes direct comparisons with

standard induction plus maintenance regimens, limiting the ability to draw definitive conclusions regarding the relative efficacy of the two induction courses. Furthermore, the use of landmark analysis to assess RFS and CSS only at the timepoint 7.5 months post-induction BCG therapy means that cases of early recurrence following BCG were not assessed, potentially selecting BCG-sensitive cases. This study also lacked detailed reporting of adverse effects, which is crucial for a comprehensive assessment of the safety profile of the regimen. Future research should address these limitations to validate and extend the promising results of this study.

Potential clinical implications and future direction

The results of this study could influence the current treatment for NMIBC, potentially leading to updates that optimize BCG induction courses and maintenance schedules. Larger multicenter trials including a control group are required to validate these findings across more diverse populations. Additionally, the identification of biomarkers to predict the response to BCG therapy is crucial, as it could facilitate the development of personalized treatment protocols and tailoring therapy based on individual patient characteristics, such as age, comorbidities, and previous response to BCG.

Furthermore, the limitations of BCG therapy underscore the need for alternative or adjunct treatments. It is thus essential to investigate other immunotherapeutic and chemotherapeutic agents as potential alternatives or adjuncts to BCG. Future studies should explore the mechanisms underlying the enhanced responses observed during the two induction courses to provide deeper insights into optimizing BCG therapy and improving its efficacy. A significant limitation of this study was the lack of quality-of-life (QOL) assessments, which are critical to understanding the broader impact of treatment. Future trials should incorporate QOL measures to evaluate how treatment affects patients' overall well-being and identify approaches that balance oncologic outcomes with patient-centered care. Ultimately, these efforts could lead to more effective and personalized treatment strategies for patients with high-risk NMIBC, improving clinical outcomes substantially.

Conclusions

This study provides preliminary evidence that an extended induction course of BCG may be an effective treatment strategy for managing high-risk NMIBC particularly during BCG shortages. However, larger multicenter phase III trials comparing this approach with standard BCG therapy with maintenance are needed to properly elucidate the role of an extended induction course of BCG.

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Footnote

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