Perspective Article

From plague to the promise: The journey of Bacille Calmette–Guérin

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Abstract

Background: Intravesical Bacille Calmette–Guérin (BCG) therapy is a widely adopted treatment for non-muscle-invasive bladder cancer (NMIBC). Despite its extensive use, the historical origins of BCG therapy remain under-appreciated by many practitioners. Initially developed as a tuberculosis vaccine by Albert Calmette and Camille Guérin in the early 20th century, BCG's immunomodulatory potential was later harnessed for cancer treatment. The unintended discovery of its attenuated virulence, combined with extensive subsequent research, laid the foundation for its clinical application in bladder cancer. Currently, BCG is a cornerstone treatment for NMIBC, particularly in high-risk cases, and has significantly influenced the evolution of modern immunotherapies, including checkpoint inhibitors. **Objective:** This paper was written with the intent of exploring the origins of BCG and historically significant research that led to it's use and acceptance as a treatment for NMIBC while highlighting it's impact on the development of immunotherapy as a whole. **Conclusion:** The BCG vaccine's journey from a tuberculosis preventive to a groundbreaking cancer treatment underscores the interconnected nature of scientific discovery and its enduring impact on modern medicine.

Keywords: Bacille Calmette–Guérin, Bladder cancer, Historical development

1. INTRODUCTION

Immunotherapy is one of the most dynamic and rapidly evolving fields in medicine. Long before the advent of modern immune checkpoint inhibitors, tyrosine kinase inhibitors, and other novel agents, intravesical Bacille Calmette-Guérin (BCG) emerged as a groundbreaking treatment. The origins of BCG and its use for non-muscle-invasive bladder cancer (NMIBC) can be traced back to the foundational advancements in microbiology during the 1800s [1,2]. Introduced in the 1970s, BCG preceded many other immunomodulatory therapies due to successful implementation and demonstrated the ability to eradicate bladder cancer in up to 70% of patients [3,4]. The development, implementation, and ultimate success of intravesical BCG as a cancer therapy paved the way for a new era in oncologic treatment. The BCG vaccine was not only revolutionary in its application to bladder cancer but also continues to influence current treatment modalities. Despite its widespread use, many urologists remain unaware of its rich historical background. This paper aims to explore the history of the BCG vaccine and its journey toward becoming a pivotal treatment for bladder cancer.

2. AN ACCIDENTAL SUCCESS

In 1900, Albert Calmette and Camille Guérin sought to build upon the work of Robert Koch by developing a vaccine to prevent symptomatic infection caused by one of the deadliest pathogens of the 19th century: *Mycobacterium tuberculosis* [1-3]. Their breakthrough in creating a vaccine for the disease was, in part, accidental [2]. When culturing isolated *Mycobacterium bovis*, Calmette and Guérin attempted to reduce its tendency to clump together by adding ox bile to the bacterial growth medium. They observed that this intervention decreased the virulence of the bacteria. Nineteen years later, after 230 rounds of sequential culturing, Calmette and Guérin had produced a bacterial strain incapable of causing progressive symptomatic disease. By 1921, the vaccine was used in humans for the 1st time, achieving great success with no reported side effects [2,3].

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3. VACCINE ACCEPTANCE

In the wake of this success, there was a drastic increase in the use of the tuberculosis vaccine across Europe. By 1928, over 114,000 infants had been vaccinated [2]. Following World War II, growing concerns about tuberculosis prompted trials in both the United States and Great Britain to assess the vaccine's efficacy for primary prevention [2,5]. Initial large-scale trials using different vaccine strains yielded mixed results, leading to vaccine adoption by most of the world, while the United States initially opted to forgo its implementation. Today, the BCG vaccine remains the best option for preventing severe forms of tuberculosis, with United Nations Children's Fund continuing to supply it to much of the modern world [1,2,5].

4. BACTERIA AND CANCER

While the BCG vaccine was under development, researchers began hypothesizing about the immunomodulatory effects of bacteria and their potential role in cancer treatment. In 1909, William Cooley published a study based on observations that, in some cases of inoperable sarcoma, patients achieved complete remission following infection with erysipelas [6]. The results sparked significant interest, as Cooley described a reproducible reaction characterized by decreased tumor vascularization and adherence to surrounding tissues, necrosis of tumor tissue, and eventual disappearance of the tumor. This line of research culminated in a 1929 study, which found that among autopsied patients, there was a decrease in tumor incidence in those infected with tuberculosis [7]. Specifically, malignancy was observed in only 6.6% of patients infected with tuberculosis, compared to 16.6% of those without the infection.

5. IMMUNOMODULATION WITH BCG

Having explored both the effects of tuberculosis infection and bacterial toxin administration on cancer, scientists in the mid-1900s turned to the BCG vaccine as a potential cancer treatment. In 1959, Dr. Lloyd Old, widely regarded as the father of modern tumor immunology, published a study demonstrating that administration of the BCG vaccine limited the progression of implanted tumors in mice [8]. Not all tumor lines were equally inhibited; however, mice injected with S-180 at 14, 25, and 67 days after BCG infection exhibited complete resistance to tumor growth. Studies by Zbar and Rapp [9] in the 1970s confirmed that BCG could be used as a cancer treatment and identified parameters necessary for its effective application [9]. Importantly, their observations led to the formulation of the following four requirements for successful treatment [1,9,10]:

(i) The tumors being treated must not be too large, either individually or collectively.
(ii) A sufficient number of BCG bacteria must be injected into the tumor.
(iii) BCG bacteria must be in close proximity to the tumor for optimal effectiveness.
(iv) The host must have sufficient immune capability to mount a response to the BCG vaccine.

6. PUSHBACK AND PERSEVERANCE

The proof of concept established by research into the immunomodulatory effects of the BCG vaccine demonstrated its potential as a cancer treatment and laid the foundation for its therapeutic use in humans. However, not everyone was optimistic about treating tumors with the BCG vaccine [11]. In 1972, Dr. Alvaro Morales requested funding for research involving the use of BCG as an immunotherapy, but he was told that the concept "was a throwback to the stone age of tumor immunology."[11, p1] Despite this setback, he published a landmark study in 1976 on the use of BCG in bladder tumors [10]. In the years leading up to his study, several papers had explored the concept of treating bladder tumors using intravesical instillation of various substances, including epodyl, yttrium-90, and thiotepa. Dr. Morales sought to combine this approach with the promising results regarding BCG's inhibition of tumor growth. He proposed that intravesical instillation of BCG could meet the qualifying criteria for successful immunotherapy outlined by Zbar and Rapp. Importantly, Dr. Morales emphasized "freedom from major systemic side effects."[12, p1] Interestingly, the study included only nine patients with a history of, or current, bladder tumor recurrence. These patients were divided into two groups based on whether endoscopic eradication of the bladder tumor had been achieved.

7. THE NUMBERS, PAST AND PRESENT

In the study by Morales *et al*. [10], each patient underwent a regimen of 1 weekly intravesical instillation for 6 weeks. Dr. Morales chose this regimen primarily because the BCG used was supplied in boxes containing six vials each [11]. Preliminary results showed that, following treatment, cancer recurred only once per 41 patient-months, compared to an average of one recurrence every 3.5 patients/months before treatment [10]. The study was a resounding success. The characteristics of NMIBC, combined with the intravesical administration of BCG, produced a treatment regimen that met the criteria for successful immunotherapy, yielding remarkable results.

8. RECURRENCE AND MAINTENANCE

Following the success of the pilot study, Dr. Morales conducted a larger randomized controlled trial [1,13]. In this study, patients with recurrent superficial bladder cancer were randomly assigned to receive either intravesical BCG

or a placebo after transurethral resection of the bladder tumor (TURBT). The trial demonstrated a significant reduction in tumor recurrence in the BCG-treated group compared to the placebo group. This study provided robust evidence supporting the efficacy of BCG in preventing bladder cancer recurrence, paving the way for its broader acceptance in clinical practice. During the same period, Lamm and Morales [1]. investigated the role of maintenance BCG therapy, in which BCG was administered not only as induction therapy but also in repeated cycles over several years. Their findings demonstrated that maintenance BCG therapy significantly reduced the recurrence rate of superficial bladder cancer compared to induction therapy alone. Ultimately, the cumulative data from these and other studies provided the necessary clinical evidence for the United States Food and Drug Administration (FDA) to approve BCG for the treatment of NMIBC in 1990 [14]. Notably, it was during this time that the story of the BCG vaccine came full circle [1]. A letter written by the daughter of Professor Guérin to Dr. Morales in 1988 detailed how she had undergone treatment for a bladder neoplasm using the same vaccine created by her father, Camille Guérin. The treatment was successful, with 24 instillations of BCG over nearly 2 years, resulting in no cancer recurrence. The treatment of NMIBC has evolved significantly since FDA approval, yet the BCG vaccine remains the cornerstone of cancer immunotherapy [3]. Common usage entails its combination with TURBT for cases of high-risk NMIBC, including carcinoma *in situ* and Ta or T1 tumors [3,15].

9. HYPOTHESES AND NEW FRONTIERS

The principles of immune activation and the importance of localized treatment strategies learned from BCG therapy have informed the design of modern treatments and will continue to do so for years to come. Investigations have explored the use of BCG as an intralesional therapy using strains including Tice, Connaught, and Tokyo-172, with Tice being the only strain currently approved in the United States [16]. Recombinant BCG variants have shown promise, with the potential to provide increased immunogenicity. Building on the clinical understanding gained from BCG, researchers have developed more sophisticated immunomodulatory therapies, such as checkpoint inhibitors (*e.g*., pembrolizumab and nivolumab), that target proteins used by cancer cells to evade immune detection [17-19]. These therapies, now widely used in various cancers, including melanoma, lung cancer, and kidney cancer, were influenced by the principles learned from BCG therapy, namely, that immune activation can lead to sustained anti-tumor effects. Additionally, the experience gained from the use of BCG has informed the development of other intravesical therapies, such as viral-based immunotherapies and novel cytokine-based treatments, designed to enhance the immune response within the tumor microenvironment. These advancements have expanded the arsenal of cancer treatments, allowing for more personalized and effective therapies that target the immune system's specific interactions with different types of cancer. These innovations are poised to complement or replace BCG in certain patient populations, offering hope for more effective and personalized treatments for NMIBC and cancer as a whole.

10. CONCLUSION

The BCG vaccine's use in treating NMIBC represents one of the most impactful developments in the history of cancer immunotherapy, rooted in scientific advances that date back over a century. Although it is a commonly used treatment, many are unaware of how the BCG vaccine's development and transition to a cancer treatment was a groundbreaking achievement that reflects the innovative spirit and the interconnectedness of scientific discovery [1,3]. The historical significance of BCG extends beyond its immediate impact on bladder cancer treatment. The success of BCG immunotherapy has had a ripple effect, influencing the development of other immunomodulatory therapies that are now at the forefront of cancer treatment [1,17]. The BCG vaccine's journey from a tuberculosis prevention tool to a cornerstone of cancer immunotherapy is a testament to the enduring impact of early scientific discoveries on modern medicine. It has not only provided a life-saving treatment for patients with NMIBC but has also laid the groundwork for a new era of cancer treatment that continues to evolve. As we look to the future, the lessons learned from BCG therapy will undoubtedly continue to shape the development of innovative treatments, offering new hope to patients in the fight against cancer.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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