

Review Article

BCG Immunotherapy for Bladder Carcinoma

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Abstract

Purpose: We reviewed the literatures to see history, regimen of BCG and how BCG become a standard therapy for bladder carcinoma. **Materials and Methods:** We reviewed the previous literature describing the bacillus Calmette-Guerin (BCG) vaccine as an anticancer agent and its success as the most effective immunotherapy used against human bladder cancer and its adverse effects. **Results:** The association between tuberculosis and carcinoma is well established, It demonstrate that Bacillus Calmette-Guerin have immunological reactivity, inhibiting the tumor growth and progression in experimental animal models, led to clinical trials showing that intravesical Bacillus Calmette-Guerin eradicate and prevent recurrence and progression of superficial bladder carcinoma. The exact mechanism of action of intravesical BCG instillation is still under investigation. However, it appears that BCG is mediated by the local immune response, mainly through T-helper cell response. It reduces the recurrence rate by an average of 40% and progression by more than 20% in papillary tumors, Carcinoma-in-situ over the patients without BCG therapy. **Conclusions:** For the last 45 yrs Bacillus Calmette-Guerin therapy has remained first line intravesical immunotherapy for superficial bladder cancer, an outstanding example of successful immunotherapy.

Keywords: BCG immunotherapy, Urinary bladder carcinoma, Intravesical instillation.

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Introduction

Adjuvant Intravesical BCG immunotherapy is one of the main modalities for superficial bladder carcinoma. Bacillus Calmette-Guérin (BCG), a live attenuated strain of Mycobacterium bovis, is currently the only agent approved by the US Food and Drug Administration for primary therapy of superficial bladder carcinoma and carcinoma- in-situ. Other agents have been used in bladder cancer. It is nearly 45 years since Bacillus Calmette-Guerin therapy has remained the most effective local therapy for superficial bladder cancer, an outstanding example of successful translational medicine in urology. The aim of this systematic study was to review history of BCG for bladder carcinoma, available evidence on the action of

BCG and optimal dose on bladder carcinoma with adverse effects. A literature search within the Medline and Pubmed was conducted with the following search terms: History, mechanism of action of BCG on bladder cancer, optimal dose, side effects for published data in the English language from 2010 to 2017 to review the current status of intravesical therapy of BCG. Thirteen relevant original articles were identified, including 6 articles directly presenting the safety and efficacy of BCG therapy in patients with superficial bladder carcinoma were selected for review. Numerous studies have set out to explain how BCG exerts antitumor effect. Many clinical applications have attempted to address optimal dose relating to BCG immunotherapy, dosing regimens, induction and maintenance therapy,

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comparison with other cytotoxic chemotherapeutic agents and combination therapy as (IFN)-alpha 2. For intravesical administration of antitumor agents, urinary bladder is an excellent and suitable hollow organ with a ready-made access route-urethra. Antitumor agents administration inside bladder and later voiding, thus minimizing, although not completely preventing, toxic systemic effect. Proven effects of BCG in reducing recurrence and progression have revolutionized the treatment of malignancy. This review summarizes the evidence to date and also looks at future prospects for the use of immunotherapy for bladder cancer. Most acceptable dose, induction treatment and maintenance therapy protocols are discussed. However, these are yet to be confirmed in large randomized trials.

How BCG came to use in bladder carcinoma ?

Bacillus Calmette-Guérin is an attenuated mycobacterium developed from the Mycobacterium bovis strain which has been used for protection for tuberculosis for more than 90 years. It is a live attenuated vaccine originally produced from the same bacterium that gives rise to bovine TB, ie, Mycobacterium bovis. Attenuation was achieved through manipulation of the bacillus by serial growths on a culture medium. This resulted in a gradual loss of the genes producing virulence such that it could be safely inoculated into humans¹. At the beginning of the 20th century, it became known that TB patients were less likely to contract cancer. An autopsy series was one of the first reports that documented a lower frequency of cancer in patients with TB². The mechanism is unclear. Apparently the disease had an antitumor effect. The first clinical trial using BCG in acute lymphoblastic leukemia was reported by Mathe et al. in 1969. In 1976, Morales, Eidinger, and Bruce were the first to report on successful treatment of superficial bladder cancer with intravesical BCG³. They were able to demonstrate a remarkable decrease in the rates of recurrence in 9 patients. A randomized prospective trial by Donald Lamm and associates in 1980 confirmed these earlier observations⁴.

In the 1930s, the use of BCG as a cancer therapy was first raised, gradually it has been using as immunotherapy for superficial bladder carcinoma.

Mechanism of Action of BCG

The mechanism of action of BCG therapy is incompletely understood. Some early studies purported that an immune response against bacillus Calmette-Guérin (BCG) surface antigens cross-reacted with

putative bladder tumor antigens, and this was proposed as the mechanism for the therapeutic effect of BCG; however, multiple subsequent studies denied this claim. Once BCG in the bladder, the live organisms enter macrophages, where they induce the same type of histological and immunologic reaction was found in patients with tuberculosis. BCG vaccine also has been shown to have a predilection for entering bladder cancer cells, where the proteins are broken down and fragments are combined with antigens and displayed on the cell surface. This induces a cytokine and direct cell-to-cell cytotoxicity response, which targets tumor cells for destruction⁵.

However, other idea is that the profound effect of BCG on stimulation of the immune system is well recognized^{6,7}. Evidence to date supports the idea that the antitumor effects of BCG are produced by an interplay between the direct effects on tumor cells by BCG infection and the host's immune response⁸. BCG therapy seems to be the binding of mycobacteria to the urothelial lining, which depends on the interaction of a fibronectin attachment protein on the bacterial surface with the fibronectin in the bladder wall. The presence of BCG then leads to the activation of urothelial and antigen-presenting cells⁹. Evidence to date supports the idea that the antitumor effects of BCG are produced by an interplay between the direct effects on tumor cells by BCG infection and the host's immune response⁸.

This action results in a massive local immune response (immunotherapy) characterized by induced expression of cytokines in the urine and bladder tissue, and an influx of granulocytes as well as mononuclear cells into the bladder wall. After these events, a massive cellular infiltration is seen, and this local inflammatory reaction in the bladder mucosa is characterized by large numbers of T cells, both CD4 and CD8, as well as macrophages². The result of this immune activation is to improve recognition and subsequent destruction of tumor cells through non-specific and specific cell-mediated mechanisms⁹. Only viable BCG organisms can induce the activity of the killer cells. This fact may explain why live attenuated BCG is necessary for successful intravesical BCG therapy¹⁰. Several cytokines have been implicated in this cell-mediated response, including interleukin (IL)-1, IL-2, IL-6, IL-8, IL-10, IL-12, tumor necrosis factor- α , and IFN.¹¹ This has been demonstrated by analysis of urine following administration of BCG. IL-1, IL-6, and IL-8 are increased after the first BCG instillation^{12,13}.

There is increasing evidence to support the role of neutrophils in BCG immunotherapy for bladder cancer¹⁴. Neutrophils are the major white blood cell component present in urine following BCG therapy, the degree of which appears to predict tolerance and outcome of intravesical BCG immunotherapy¹⁵. Saint et al showed that a high leukocyturia count following BCG correlated with a reduction in recurrence. The preliminary results of this study suggest that the degree of leukocyturia might be used as a means by which to adapt BCG maintenance regimes to the individual patient¹⁵.

Macrophages have also been identified as likely cell types involved in BCG-induced antitumor activity^{16,17}. There is now a large body of evidence demonstrating the superior efficacy of BCG in the treatment of bladder cancer when compared with TUR alone or TUR and chemotherapy. Comparing of BCG with epirubicin and IFN,¹⁸ mitomycin C,¹⁹ and epirubicin alone,²⁰ all of which showed BCG to be the best agent with respect to preventing recurrence. A recent review has shown that it is predominantly a T-helper/inducer cell-mediated response with persistence of inflammatory (Th1-type) cytokines for a long time within the so-called BCG-induced granulomas, which might have an important role in the recurrence-free status of the patient²¹. This prolonged inflammation seems to provide immature effector cells with a continuous level of activating cytokines (such as IL-2, Interferon- γ and IL-12)²².

Standard BCG treatment protocol

Standard treatment consists of a once-weekly instillation of BCG for 6 weeks. Patients are given live attenuated BCG mixed in 50 mL of normal saline, instilled into the bladder via a urethral catheter. The patient retains the fluid within the bladder for an hour, and during this period the patient lies prone for 15 minutes, supine for 15 minutes, and on each side for 15 minutes. Caution is suggested in handling the BCG because of a small risk of TB infection. The staff administering the BCG should be suitably protected with masks, goggles, gloves, and gowns to avoid inhalation and contact of BCG with broken skin. All equipment, supplies, and receptacles in contact with BCG should be handled and disposed of as biohazardous materials. Patients should be advised to pour 2 cups of household bleach into their toilets after urinating to neutralize any BCG that may be found in the urine. The medication and bleach should remain in the toilet for 15 to 20 minutes before flushing. Patients should be advised to wash their hands and

genital areas thoroughly after urinating and to drink plenty of fluids after each installation to flush the bladder.

After the conclusion of the 6-week course, the patient undergoes a cystoscopy. If the bladder is free of tumor recurrence, then the patient is entered into a program of regular cystoscopic follow-up. If the tumor recurs, then the patient can, after resection, have a further course of BCG². The dose of BCG is reduced to 1/3, 1/10, 1/100 as needed to prevent increased side effects. Avoid giving a second 6-week course of BCG to patients who had previously received BCG, because they are at risk of immunosuppression. The addition of interferon appears to reduce this risk. When induction is completed, a course of maintenance therapy is applied. Prolonging the course of therapy has been shown to reduce the frequency of recurrence and progression. These intervals have varied from monthly to every 3 months or every 6 months. The optimum frequency and duration of this therapy seem to vary, but one study found that 2-3 installations every 3 months are effective²¹.

Most experts agree that a maintenance program of at least 1 year is necessary. From the immunologic point of view, establishing this interval is difficult because patient variability is great and this is a biologic product whose dose may differ slightly with each installation. The potential role of monoclonal antibodies in the treatment of bladder cancer has been highlighted by recent research involving manipulation of the immune system in metastatic bladder cancer. This has shown the promising result, but its potential role in BCG-refractory superficial disease remains unclear. Further experimental and clinical research is required to test these theories and techniques, and it is hoped that new research may result in effective therapies in near future. As the understanding of the immunological response to BCG in the urothelium and tumor cells develops, several candidates, are being identified which may support the development of future targets for immune-based therapies.

Side effects of BCG

Generally speaking, BCG is fairly well tolerated but can be fatal²⁰. Specific side effects are common. The most frequent are abacterial cystitis and dysuria, hematuria, and a low-grade pyrexia. The primary side effects of BCG are increased urinary frequency, dysuria, hematuria, and flu-like symptoms.

Systemic symptoms can include arthralgia/arthritis, rash, fatigue, fever, and systemic BCG infection, which can present as pneumonitis, hepatitis, epididymitis, prostatitis, renal abscess, or sepsis. BCG induces an anti-tumor response in bladder cancer by drawing lymphocytes and macrophages to the bladder and stimulating a cellular (TH1) immune response. Cytokines associated with this response result in symptoms of bladder inflammation and even flu-like symptoms. Patients who have a fever associated with BCG have a lower risk of tumor recurrence, but fever and increasing local symptoms can also herald a severe BCG reaction. Therefore, we recommend the policy of reducing the dose of BCG in patients with increasing side effects. These side effects usually subside within a 48-hour period and require little more than an analgesic for treatment. In these cases, BCG treatment can continue, but if the side effects are troublesome, increasing the time between treatments or reducing the dose should be considered. Contraindications include an impaired immune response caused by disease, drugs, or other therapy; pregnancy and lactation; and positive HIV serology. In order to reduce the potential side effects of BCG, studies have explored the impact of a reduced dose on both efficacy and toxicity^{22,23,24,25}.

This review draws the attention to the fact that some of the suggested methods to prevent BCG toxicity are no longer valid. An important suggestion is to give written information to patients and their guardians on the possible severe early and late complications in any organ of the body. Although it has not been proved, it seems a method of common sense to improve early detection and therapy²⁶. When BCG vaccine therapy was introduced, several deaths were reported, all of which could be attributed to improper use of this agent. At present, a death is extraordinary because clinicians have learned how to administer this agent and to stop therapy before a patient becomes²⁷.

Conclusion

This review suggests that BCG is an effective immunotherapy for superficial bladder carcinoma. Although it has many toxic effects, which can be managed properly, an optimal dose selection is still necessary. Many research has done regarding the mechanism of action and suggested many theories, still more research is needed to setup an optimal dose and mode of action of BCG for superficial bladder

carcinoma. According to authors experience, it is questionable, whether neoadjuvant immunotherapy will be effective to reduce the size of bladder tumor later on effective resection in selective cases.

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