What have we learned after 30 years of BCG intravesical therapy for superficial bladder cancer?

O que nós aprendemos após 30 anos de terapia intravesical com BCG no tratamento do câncer de bexiga superficial?

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ABSTRACT

Objectives: To discuss the role of bacillus Calmette-Guérin (BCG) immunotherapy in the treatment of superficial bladder cancer after 30 years of clinical experience. Methods: Research on LILACS and PubMed databases, including 31 clinical studies with scientific relevance and importance in the decision-making process. Results: The BCG therapy with induction and maintenance therapy seems to be the best practice in tumors classified as high risk when compared to intravesical chemotherapy. In management of carcinoma in situ, BCG is undoubtedly the therapy of choice, presenting 84.4% of efficacy. As an adjuvant treatment to transurethral resection, there was a 31% reduction in recurrence confirmed in four out of five meta-analyses assessed. The reduction in progression, despite preliminary favorable evidence, still needs further studies to be confirmed. Conclusions: Intravesical BCG is an excellent therapeutic option in cases of carcinoma in situ and it is recommended as an adjuvant treatment in tumors with a high risk of recurrence and progression.

Keywords: Urinary bladder neoplasms/drug therapy; Immunotherapy; BCG vaccine/therapeutic use; BCG vaccine/administration & dosage

INTRODUCTION

The use of bacillus Calmette-Guérin (BCG) as a therapeutic alternative in oncology was first described in 1930. Despite causing remission in several types of tumors, the high toxicity observed on BCG injection was not a factor for stimulating the progress of this therapy.

In 1976, Morales described an intravesical BCG regimen which maintained a good antineoplastic
response and significantly reduced the systemic effects. Since then, intravesical therapy with BCG has been widely used after transurethral resection (TUR) as an adjuvant treatment to prevent recurrence of bladder cancer, which is the second most frequent malignant neoplasm of the genitourinary tract and represents about 1 to 3% of all tumors diagnosed\(^{(1-2)}\).

Although it has been used for more than 30 years, there are no equivalency studies among the seven existing strains and there is no consensus about the ideal dose to be used. The probable mechanisms of action of BCG were determined in experimental research. In this setting, treatment is still empirical.

Time has shown that the adjuvant therapy with BCG in urinary bladder cancer indicated its benefit in patients with a higher risk of recurrence and particularly in cases of carcinoma in situ (CIS). A recent meta-analysis showed that treatment with BCG has the potential to reduce both risk of recurrence and progression in patients with superficial bladder cancer\(^{(3)}\).

Immunotherapy with BCG has also been gaining more acceptance in treatment of urothelial carcinoma of the upper urinary tract with renal preservation\(^{(4)}\).

Although not much frequent, systemic complications of intravesical administration of BCG may produce potentially severe effects. Several studies have been conducted to increase the efficacy and reduce the side effects.

**OBJECTIVE**

To carry out a review to compile the main studies about BCG that have guided the clinical practice of urologists treating the bladder tumors.

**METHODS**

This article was based on a bibliographic review by means of databases available on the Internet – PubMed and LILACS, in addition to textbooks. The following keywords were used: bacillus Calmette-Guérin, intravesical therapy, bladder cancer, immunotherapy, clinical trial.

The inclusion criteria used were any articles, regardless of design (double-blind, case control, randomized or not) addressing phase I or phase II studies about efficacy and/or treatment regimen of BCG. The exclusion criteria took into account articles about treatment of superficial bladder cancer related to other therapies except BCG.

Fifty-one articles about the subject were identified and, based on the inclusion criteria, a total of 31 articles were selected.

**RESULTS**

Eight original articles with prospective studies were found, as well as seven original articles with randomized studies, six review articles, four meta-analysis articles, three multicenter trials and three textbook chapters.

The approach included the aspects related to treatment schedule and efficacy according to indication, understanding the treatment of CIS, papillary tumors, prophylaxis of tumor recurrence and disease progression.

**DISCUSSION**

**TREATMENT REGIMEN**

Adjuvant treatment with BCG must be indicated according to the cost-benefit ratio. Not all patients with superficial bladder cancer should be treated with BCG. The risk of tumor recurrence defines the choice of treatment administration or not (Chart 1).

<table>
<thead>
<tr>
<th>Group of risk</th>
<th>Adjuvant treatment after transurethral resection</th>
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<tbody>
<tr>
<td>Low risk</td>
<td>One immediate chemotherapy instillation</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>Intravesical chemotherapy or BCG</td>
</tr>
<tr>
<td>High risk</td>
<td>Intravesical BCG</td>
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BCG administration can be percutaneous, intralesion injection, oral, combined intravesical instillation and percutaneous administration, and isolated intravesical instillation. The first three options were abandoned due to morbidity, severe side effects and inefficacy, respectively\(^{(5)}\). There is no difference in efficacy between the last two routes, although isolated instillation is the standard treatment\(^{(6-7)}\).

The dose, ideal number of instillations, frequency and duration of instillation maintenance remain unknown. The method described by Morales\(^{(8)}\) consists of a weekly instillation during six weeks, which was conventionally called induction cycle.

Different maintenance schedules have been applied, varying from 10 instillations for 18 weeks to 30 instillations for 3 years\(^{(9)}\).

To reduce toxicity, some urologists propose dose reduction to one-third or up to one-fourth of original dose. In the evaluation carried out with 500 patients by the Spanish cooperative group called Club Urológico Español de Tratamiento Oncológico (CUETO), although some patients had lower toxicity, the incidence of severe systemic toxicity was similar both with full dose and with administration of one-third of the ideal dose\(^{(10)}\). The European Organisation for Research and
Treatment of Cancer (EORTC) conducted a phase II trial with 44 patients who achieved 61% of complete response with one-fourth of the ideal dose\(^{(11)}\). As to BCG variations, Tice, Pasteur, Connaught, RIVM and A. Frappier, there is no difference shown in the capacity of each one to prevent tumor recurrence and progression\(^{(9)}\).

BCG is administered by means of an instillation of attenuated tuberculosis bacilli mixed in 50 ml of saline solution in the urinary bladder by a urethral catheter. The patient must retain the fluid in the bladder for one to two hours. It is important to check that the bladder is empty before instillation and that urethral catheterization has been performed without traumatism.

Some authors advocate that during this period the patient should alternate the position every 15 minutes in pronation, supination and lateral decubitus\(^{(12)}\). This would guarantee that the whole mucosa is reached by the solution.

The risk of tuberculosis infection is low and patients are instructed to disinfect the bathroom after urinating to neutralize any trace of BCG that may remain in the eliminated urine.

After completing six weeks of treatment, patients undergo cystoscopy. If the bladder is free of tumor recurrence, then regular cystoscopy is performed for follow-up. In case of recurrence, a new resection is performed and followed by a new course of BCG. In this second therapy, 20 to 30%\(^{(13-14)}\) of patients become tumor-free. However, when the second attempt also fails, only 20% become free of tumor and there is an increased risk of progression\(^{(14)}\).

BCG therapy with maintenance regimen seems to be the best management in tumors with highest risk of recurrence and progression. In the randomized protocol of the Southwest Oncology Group (SWOG), Lamm et al. showed that induction therapy followed by maintenance was better than isolated induction therapy. BCG was administered on a weekly basis for three weeks, 3, 6, 12, 18, 24, 30, and 36 months after a six-week induction with BCG. Mean recurrence was 76.8 months versus 35.6 months in those who did not receive maintenance therapy (\(p < 0.001\))\(^{(15)}\).

A meta-analysis conducted by the EORTC assessed 24 trials about therapeutic management with BCG. BCG was superior to intravesical chemotherapy for reducing recurrence in patients with a high risk of relapse. In the four trials in which BCG maintenance therapy was not administered, there was no reduction in tumor regression. In the other 20 trials using the maintenance therapy with BCG, there was a reduction by 37% in progression\(^{(16)}\) (OR = 0.63, \(p = 0.00004\)). However, Bohl et al. concluded that – to achieve the necessary effect – at least one year of BCG maintenance is required to show superiority over prevention of tumor recurrence using mitomycin C\(^{(17)}\).

Although their benefits are considered, it should be mentioned that excessively long maintenance courses show higher rates of early withdrawal from the protocol due to several reasons. In the SWOG trial, only 16% of patients completed the BCG maintenance schedule for three years\(^{(15)}\). In another randomized trial carried out by EORTC in 520 patients, about one-third completed the entire schedule, 17% discontinued due to inefficacy, 19% discontinued due to side effects and 31% discontinued due to ‘other reasons’\(^{(9)}\).

Efficacy according to indication

Successful treatment with BCG depends on its appropriate use. It is used for several reasons: to treat CIS; residual papillary tumors; to reduce the number and frequency of tumor recurrence; to prevent disease progression – although the latter is still controversial and there is no consensus about this matter\(^{(18)}\).

Treatment of CIS

High rates of response have made BCG the first line treatment for CIS. In 1995, Akasa et al. showed in a trial that 84.4% of their 32 patients had a complete response to therapy\(^{(19)}\). Harlang et al. used a lower dose of BCG in 53 patients and obtained a complete response in 53%\(^{(20)}\).

Nowadays we also know that the best responses occurred in patients with primary CIS (not related to the papillary tumor of the bladder). In a study carried out by Merz et al. in 115 patients with CIS, 25 patients had primary CIS and 90 had secondary CIS. This study showed that 88% of those with primary CIS had a complete response with negative cytological and cystoscopic findings. In patients with secondary CIS, 78% showed complete response to BCG\(^{(21)}\).

In another study, Sylvester et al. randomized 700 patients with CIS comparing BCG and mitomycin C (MMC), epirubicin, Adriamycin, or sequential MMC/adriamycin. Based on a 3.6-year follow-up, they showed that 161 out of 345 (46.7%) patients did not have evidence of disease compared to 93 out of 355 (26.2%) patients undergoing chemotherapy, a reduction by 59% in treatment rates (OR = 0.41, \(p = 0.0001\))\(^{(22)}\).

Primary treatment for papillary tumors

It is less commonly indicated, since the best responses occur when there is no detectable macroscopic tumor. It is used when the complete endoscopic control is not possible or when the patient is not appropriately prepared for a surgical procedure\(^{(12)}\).
Akasa et al. used BCG as the initial treatment in 125 cases of Ta or T1 tumors and found a response rate of 66.4%. A partial response was then found in 20.8% of patients(19).

**Prophylaxis of tumor recurrence**

Statistics showed that 40 to 70% of patients with bladder cancer will have a relapse within two years. There are several trials comparing the adjuvant intravesical therapies, but comparisons are difficult due to the different regimens and dosages used(12).

Lamm et al. reviewed the long-term results of intravesical therapies for superficial bladder cancer. They observed that four out of five comparisons between adjuvant BCG therapy and isolated surgery showed a significant reduction of tumor recurrence with the use of BCG. Recurrence was 75% in the Control Group, as opposed to 31% in the group treated with BCG. In their review of 20 chemotherapy trials, these authors observed that only 11 showed a significant reduction in recurrence. They also reported that chemotherapy had an effect in the reduction in recurrence in the first five years; after that period, the incidence of recurrence was the same as that in the group treated with isolated surgery(23).

Several studies have compared BCG and intravesical chemotherapy. Lundholm et al. randomized 261 patients with superficial bladder cancer to receive BCG or mitomycin C. After a follow-up period of 39 months, 49% of those who received BCG were disease-free versus 34% of patients treated with mitomycin C (p < 0.03)(24). This advantage of BCG compared to mitomycin C was not reported in all of the studies. Rubben et al.(25) found a difference of only 7% in their studies and Vegt et al.(26) reported that both BCG and mitomycin C were equally efficient. This absence of difference can be explained by the fact that most study groups had low grade Ta lesions, which may hide the benefit of the BCG regimen as compared to mitomycin C in patients with high grade lesions.

**Progression**

Herr et al. compared TUR and BCG with isolated TUR(27). They reported that 95% of patients treated only with TUR showed disease progression, as opposed to 53% of those treated with BCG after TUR. Metastasis occurred equally in both groups, but at a significantly later time in the group treated with BCG (p = 0.012). A high percentage (42%) of the control group underwent cystoscopy compared to 26% of the group treated with BCG and TUR (p = 0.017). It was also reported that the time to cystectomy was shorter in the control group (8 versus. 24 months) and mortality rate was 32% in the Control Group and 24% in the BCG group (p = 0.032).

Lamm et al. compared doxorubicin with BCG and found that progression was 37% in the group treated with doxorubicin versus 15% in the group treated with BCG (p = 0.015)(28).

In regard to progression, there seems to be less difference when BCG is compared to mitomycin C. Lundholm et al. randomized 261 patients to receive mitomycin C or BCG with a mean follow-up of 39 months(24). Tumor progression was similar in both groups (13%). Krege et al. compared isolated TUR, TUR with BCG and TUR with mitomycin C. Progression was 4.2% in all three groups(29). Again, the result can be explained by the large number of patients with low grade Ta tumors which can mask the benefits in terms of tumor progression in the groups treated with BCG.

A meta-analysis involving more than 2,500 patients showed that while treatment with intravesical chemotherapy delays the first episode compared to isolated TUR, it does not have any influence on the time to progression and on muscle invasion(30). Although the use of BCG is superior to chemotherapy for the prevention of recurrence, controversies still exist whether BCG could delay or prevent progression to muscle invasion(9).

Another meta-analysis assessed 24 studies with 4,863 patients and showed that the use of intravesical BCG reduces the risk of progression in papillary tumors and CIS when maintenance therapy is used. Based on a follow-up of 2.5 to 15 years, 260 out of 2,658 patients treated with BCG (9.8%) presented progression compared to 304 out of 2,205 patients in the control group (13.8%), a reduction by 27% in the progression rates in the group treated with BCG(31).

In other studies, however, decreased recurrence risk was seen only when maintenance was performed between 18 months and three years(9).

Despite the proven efficacy of treatment with BCG, some doubts still do not have appropriate responses: how can one predict if BCG will effect its response in an individual patient? Is it possible to reduce the dose without impairing the therapeutic effect? Which are the real mechanisms of action of BCG? How can one reduce the side effects? Can one use parts of bacteria with the same efficacy(10)?

Since no other drug has surpassed the efficacy of BCG, current research aims to improve its clinical use in the treatment of Ta, T1 and CIS tumors.

**CONCLUSION**

According to the present review, intravesical BCG was efficient as a therapy in cases of carcinoma in situ and its use is indicated for adjuvant treatment in tumors with high risk of recurrence and progression, in addition to primary treatment of papillary tumors. Intravesical
instillation is the standard procedure for administration of BCG and there is no ideal drug regimen due to its high toxicity.

REFERENCES