ABSTRACT

Bladder cancer is the second most common cancer in the urinary tract and the most frequent histological type is transitional cell carcinoma (TCC). Approximately 70% of these cancers are superficial (no evidence of muscle invasion) in situ (Tis), Ta and T1 carcinomas. The biological behavior of these tumors varies from slight recurrence tendency to a high degree of recurrence and progression. Although transurethral resection of the bladder tumor (TURBT) is the standard treatment, a large number of complementary treatments based on the administration of different intravesical chemotherapeutic and immunotherapeutic agents, including Bacillus Calmette-Guérin (BCG) have been established. The most appropriate management consensus has yet to be determined. The present article reviews the use of BCG in superficial bladder cancer in relation to its indications, contraindications, action mechanism and different results in distinct stages of the disease.

Key words: bladder tumors, superficial bladder carcinoma, medical treatment, BCG immunotherapy, Mexico.

RESUMEN

El cáncer de vejiga es la segunda causa más común de cáncer en el tracto urinario. El tipo histológico más frecuente es el carcinoma de células transicionales (CCT). Alrededor de 70% de estas malformaciones es superficial (sin evidencia de invasión muscular), carcinoma in situ (Tis), Ta y T1. El comportamiento biológico de estos tumores es variable, desde escasa tendencia a recurrir hasta un alto grado de recurrencia y progresión. Aunque el tratamiento estándar lo constituye la resección transuretral del tumor de vejiga (RTUTV), se ha establecido una gran cantidad de medidas complementarias basadas en la administración de diferentes agentes intravesicales, por ejemplo los agentes quimioterapéuticos y la inmunoterapia, como el bacilo de Calmette-Guérin (BCG), sin determinar aún cuál es el más apropiado. En este artículo se presenta una revisión del uso del BCG en el carcinoma superficial de vejiga, indicaciones, mecanismo de acción, contraindicaciones y diferentes resultados en sus distintas etapas.

Palabras clave: neoplasias de vejiga, carcinoma superficial de vejiga, tratamiento médico, inmunoterapia con bacilo de Calmette-Guérin, México.
INTRODUCTION

SUPERFICIAL CARCINOMA OF THE BLADDER

Cancer of the bladder is the second most common cancer in the urinary tract and is among the ten most common types of cancer in humans. Close to 70% of bladder carcinomas present with no histological muscle layer invasion of the bladder wall. The majority of these tumors are transitional cell carcinomas that have different degrees of histological differentiation (I-III). Superficial bladder cancer includes carcinoma in situ (Tis), tumor confined to the epithelium (Ta) and tumors that invade the lamina propria (T1). It is a heterogeneous disease with a variable natural history. There is low-grade Ta carcinoma with a low progression percentage and at the other extreme there is high grade T1 tumor with a high malignant potential and a significant level of progression and death from the disease. Close to 70% of superficial tumors present as Ta lesions, 20% as T1 lesions and 10% as Tis lesions. Different characteristics of these malformations, including pathological characteristics, cytological analysis and biological or molecular markers have been studied in an effort to predict their uncertain behavior.

INITIAL TREATMENT

The critical initial step is to carry out complete endoscopic resection of the visible tumors. It is imperative to include the base of the tumor in the specimen as well as part of the muscle layer of the bladder wall in order to obtain adequate histological information. Sixty to seventy percent of superficial bladder tumors recur and 20-30% of these tumors progress to a higher stage or grade. Adjuvant therapy following initial surgical treatment of these tumors has been necessary due to the high recurrence percentage and unpredictable progression pattern of the disease.

INTRAVESICAL THERAPY

The objectives of applying medication within the bladder cavity are:

1.- To eradicate the existing disease that could not be controlled endoscopically, such as carcinoma in situ - a process that is generally diffuse - or when the base of a papillary tumor is large and cannot be completely resected.

2.- To prevent recurrence in at-risk patients. Some factors are recurrence-predictive such as degree of tumor depth, multiplicity, tumor size, presence of concomitant Tis and time between tumor and its first recurrence.

3.- To prevent progression in at-risk patients. Progression is defined as the development of muscle invasion or metastasis. Progression presents in 20-30% of superficial bladder tumors. There are also predictive progression factors such as tumor grade, lamina propria invasion and presence of Tis.

Over the years different intravesical cytotoxic agents have been used such as thiotepa, mitomycin C, doxorubicin and epirubicin. The role of intracavitary chemotherapy is well-defined. However, there is no consensus as to which is the best medication, application regimen and dosage to be used.

DEVELOPMENT OF BCG

What is BCG? BCG vaccine is a culture of weakened live bacteria of the tuberculosis bacillus. In 1904 Nocard isolated the Mycobacterium bovis from tuberculous mastitis in a cow. In 1908 Albert Calmette and Camille Guérin were able to make cultures of this bacterium gradually lose their virulence and after 231 cultivated generations over a period of 13 years they obtained completely avirulent strains. This special M. bovis strain was given the name bacillus Calmette-Guérin or BCG.

Different sub-strains have been created since 1921 and distributed to many countries. The most widely used strains today are the Connaught, Pasteur,Tice and Tokyo strains.

In 1929 Pearl was the first to suggest using BCG as a therapy for cancer after observing that cancer was less frequent in TB patients. In 1935 Holmgren treated cancer patients with tuberculin and BCG and reported variations in tumor regression. Unfortunately, a year later the tragedy known as the Lübeck disaster occurred due to a laboratory mistake and more than 70 German children who were vaccinated with a virulent strain of the tuberculous bacillus died from the disease. Thirty years had to pass before interest was once again directed at the antineoplastic properties of the vaccine.

In 1966 Coe and Feldman demonstrated that the bladder was capable of reacting to antigenic stimulus with a delayed hypersensitivity making it the ideal organ for local immunotherapy. This created the theoretical rationale for topical intravesical immunotherapy.

In 1970 Morton described malignant melanoma regression after BCG intralesional injection. In 1971 the systematic work of Zbar at the National Cancer Institute in the United States was of vital importance for future BCG applications in oncology. He used a hepatocarcinoma animal model to demonstrate that BCG administration in tumor cells led to significant regression.
inhibition of tumor growth. He also established basic rules for optimum immunotherapy with BCG in tumors: there is a better response in localized tumors than in disseminated tumors, tumor should be the smallest size possible before beginning immunotherapy and there should be direct contact for the appropriate amount of time between tumor cell and BCG. He also indicated that the effective optimum BCG dose for local or intratumoral application was from $10^6$ to $10^8$ colony forming units (CFU).

In 1976 Morales reported that all of these conditions for BCG immunotherapy were present in superficial bladder cancer and demonstrated a recurrence reduction in nine treated patients.

In 1990 the Food and Drug Administration (FDA) approved the use of BCG for treating superficial bladder cancer.

ACTION MECHANISM

What takes place in the bladder after intravesical BCG instillation? Immunotherapy with BCG provokes a massive local immune response characterized by induced cytokine expression in urine and bladder tissue and a migration of monocytes and granulocytes as well as mononuclear cells to the bladder wall.

At the moment of BCG intravesical instillation, BCG is attached to the urothelium through fibronectin. By remaining in contact for the appropriate amount of time with the bladder wall, monocytes and granulocytes found there phagocytose the bacilli thus activating intracellular production of an important variety of cytokines. Among them is tumor necrosis factor-α (TNF-α) that stimulates colonies of granulocytes, interferon-gamma (IFN-γ), interleukins (IL) IL -1, IL-2, IL-5, IL-6, IL8, IL-10, IL-12 and IL18 as well as the development of membrane antigens such as HLA-DR and intracellular adhesion CD25 and molecule 1. The production of membrane antigens within the monocytes also takes place in the urothelium, expressing the major histocompatibility class II complex (MHC-II). The presence of membrane antigens in the monocytes activates CD4 helper cells and these produce IL-2 and IFN-γ, which in turn activate effector cells or natural killers (NK). Once these cells are activated, CD8+/CD16dim and CD56+ cellular subpopulations lyse the tumor by means of perforin production (Image 1).

It is important to point out that these changes in the patient’s bladder can be maintained for more than a year after first contact with the bacillus but they commonly diminish after 3-6 months, providing the rationale for maintenance therapy.

BCG USEFULNESS IN SUPERFICIAL BLADDER CANCER

DOSE

Optimum BCG dose has not been identified. However, the standard dose has been established as 120 mg per instillation session with which $10^6$CFU are obtained. This has been reported to be the minimum therapeutically effective dose (23x Zbar 71, 24x Ratliff 86).

INSTILLATION

For BCG reconstitution, 120 mg is mixed in 50 mL of saline solution at 0.9% and instilled into the bladder through a urethral catheter. Before application, urinary tract infection should be ruled out and the catheter should be introduced without causing injury. Patients should retain the liquid in the bladder for one or two hours, rotating position every 15 minutes from prone, to supine, to lateral so that the solution comes into contact with the entire bladder mucosa surface.

TREATMENT REGIMEN

Intracavitary BCG immunotherapy consists of an induction regimen followed by a maintenance regimen. Optimum BCG administration regimen has yet to be defined.

An induction regimen is necessary in order to develop immunological response in the bladder. It is begun from the second to the fourth week following transurethral resection of the bladder tumor (TURBT) and may be applied at the sixth week if necessary. The weekly application regimen for six weeks was chosen arbitrarily. The majority of patients develop adequate immunological response with six applications. Some may require fewer applications and others may require more. It has been demonstrated that a second induction cycle for another six weeks is helpful in those patients who do not respond to the first cycle.

Employing a maintenance regimen is also controversial. Initial studies on the results of this regimen applied monthly or every three months over a period of two years did not show a clear benefit that would justify the increase in adverse effects caused by the therapy itself. The most widely used maintenance regimen is that proposed by Lamm and the Southwest Oncology Group (SWOG) which is a weekly induction instillation for six weeks followed by weekly instillation for three weeks at three and six months, and then weekly instillation for three weeks every six months for three years. Other regimens include weekly intravesical
administration for three weeks at three, six, twelve, eighteen, twenty-four and thirty-six months. However, optimum application time for these maintenance doses, whether they are monthly, every three months or even annually has not been standardized.

**DOSE REDUCTION**

Efforts to reduce BCG vaccine toxicity, while at the same time maintaining a high level of efficacy, are being made today through studies in all populations of patients treated with BCG. Some studies suggest that low BCG doses that greatly reduce the toxicity of the vaccine may be as effective as the traditional dose.

A randomized prospective study by the Spanish Oncological Group revealed an important reduction in toxicity with low BCG doses that did not alter its efficacy. A total of 500 patients with TaG2-3, T1G1-3 and Tis were randomized to receive 81 mg (Connaught) vs 27 mg. Toxicity in the high dose group was much greater. There was no statistically significant recurrence (18% and 19%) or progression (2.4% and 4.8%) after mean 18.6 month follow-up. However, Tis patients in the low dose group presented with more aggressive recurrence (31% vs 12%) which makes true efficacy of low dose questionable in this type of patient. The Morales study that compared BCG instillation dose (120 mg vs 60 mg) suggests that high dose and consequent toxicity is necessary to eradicate Tis while low dose may be adequate to prevent recurrence. Mugiya et al used a dose of 40 mg of intravesical BCG in 43 Tis patients and concluded that complete response was observed in 84% of patients in whom recurrence-free percentage was 72.4% after 3 years and 61.9% after 5 years. Mean complete response was at 37.5 months and so these specialists dose indicated this dose to be effective and safe for Tis patients.

The majority of studies suggest that patients with low- or intermediate-risk tumors may benefit from reduced BCG dose but not those patients that present with high risk tumors or Tis.

**BCG FOR RESIDUAL DISEASE**

One of the best demonstrations of BCG vaccine antitumor capacity is when it is applied to patients with residual tumor due to incomplete endoscopic treatment or when it is applied as primary treatment (immunoresection) instead of endoscopic resection. While the ablative effect of an initial BCG course in residual papillary tumor varies from 15-70%, total response is consistent and at approximately 60% if at least one additional BCG course is used. These studies have shown only a marginal drop in response over time but it is difficult to evaluate due to the use of different maintenance regimens. In 2007, Hall found that recurrence in all groups at-risk for superficial bladder cancer with TURBT was only 55%, whereas by adding BCG with a single induction regimen recurrence was 36% and with maintenance therapy was 29%.
Recurrence
Tumor recurrence is defined as the development of foci of superficial tumor (Ta, T1, Tis) at any site of the bladder during follow-up. Tumor progression is defined as the development of muscle invasive tumor (T2 or higher) at any site of the bladder during follow-up.27

BCG reduces the risk of short- and long-term treatment failure compared with intravesical chemotherapy as reported by Bohle in 2003 in a comparative study of BCG vs mitomycin C in which 1421 patients were treated with BCG and 1328 patients were treated with mitomycin C and there was a mean follow-up of 26 months. Only 29% of patients treated with BCG vaccine presented with recurrence vs 46% of patients treated with mitomycin C.32 In 2005, Sylvester, after analyzing 7 randomized studies that included 203 patients with complete response, reported that 34% of those treated with BCG presented with recurrence vs 50% of those treated with chemotherapy (OR 0.47 =0.0008).33

Shahin et al. carried out a retrospective study of 153 patients with stage T1 grade 3 bladder cancer treated with intravesical BCG analyzing their recurrence, progression and survival rates. Patient total was divided into 2 groups: 92 patients treated with TURBT plus BCG and 61 patients treated with TURBT alone. A BCG dose of 120 mg remaining in the bladder for 2 hours was used. Mean follow-up was 5 years and disease recurrence was 70% in patients treated with BCG and 75% in patients treated with TURBT alone. Mean recurrence time was 38 months for those treated with BCG and 22 months for those treated with TURBT alone (P=0.19). Tumor progressed in 33% of BCG patients and in 36% in those with TURBT alone. The authors concluded that intravesical therapy with BCG after TURBT for stage T1 grade 3 patients delayed recurrence and cystectomy but did not alter the final result of the natural history of the disease.34

Progression
True progression reduction of the disease is difficult to demonstrate in individual clinical tests with BCG particularly due to the percentages of low events and prolonged follow-up times. A non- randomized Spanish protocol showed a progression relative risk reduction of 0.3 with BCG therapy. However, Solsona reported a progression percentage of 12% for BCG vs 29% for chemotherapy with a statistically significant difference; complete analysis of the two randomized tests showed an elevated relative risk for intravesical therapy.35

In the meta-analysis by Sylvester that included 24 studies with information on the progression of 4863 patients with a mean follow-up of 2.5 years, there was progression in 260 patients (9.8%) from a total of 2658 patients treated with BCG and there was progression in 304 patients (13.8%) from a total of 2205 that did not receive BCG (P=0.001), with a progression reduction range of 27% in the BCG group.36

In 2003 Peyromaure analyzed recurrence, progression and survival rates in 57 patients with stage T1 grade 3 bladder cancer with follow-up in 53 patients and a BCG regimen of 6 weeks of induction and three weeks at 3, 6, 12, 18, 24, 30 and 36 months after TURBT. He concluded that BCG therapy was effective as conservative treatment for patients with stage T1 grade 3 bladder cancer, with recurrence and progression percentages of 42.1 and 22.8, respectively.37

Free-from-disease Survival
In 2005 Sylvester analyzed 9 randomized studies of BCG vs mitomycin C, epirubicin, adriamycin and mitomycin with adriamycin and found that out of 298 patients treated with BCG, 203 (61.8%) of them had initial complete response three months after therapy compared with 158 (51.5%) treated with one of the other chemotherapeutic agents.38

Griffiths et al. analyzed bladder Tis treatment between the years of 1987-1997 in 135 patients with confirmed diagnosis. They used a 6-week BCG induction regimen. Patients were divided into three groups: 23 patients with Tis (Group 1), 37 patients with Tis associated with Ta (Group 2) and 75 patients with Tis associated with T1 (Group 3). Mean follow-up was 41 months. Percentages for complete response at three months were 74%, 70% and 75% for groups 1, 2 and 3, respectively. Mean progression percentage at 5 years was 20%, 18% and 49%, respectively. Specific cancer survival percentage was 83%, 86% and 59%, respectively. It was concluded that a BCG course is effective for primary Tis and for Tis associated with Ta but is suboptimal in patients with Tis associated with T1.39

Contraindications for BCG Therapy
Contraindications are classified as absolute and relative. The former includes immunocompromised or immunosuppressed patients; using the vaccine immediately after transurethral resection based on the risk of intravasation and septic death; personal history of BCG sepsis; macroscopic hematuria; traumatic catheterization and total incontinence. The latter


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includes urinary tract infection, hepatic disease, personal history of tuberculosis and advanced age.40

■ COMPLICATIONS

Treatment with BCG is well-tolerated in patients and minor complication incidence below 5% has been reported.41 BCG cannot be instilled immediately after TURBT due to high percentage of systemic complications. Local complications consist mainly of voiding symptoms and local irritative symptoms. Systemic complications of BCG immunotherapy are less common and usually occur after traumatic catheterization and during recurrent cystitis. Fever is reported in 2.9% of patients, arthralgia in 0.5% and sepsis in 0.4%.42,43

The following uncommon distant organ complications have been reported: BCG-related hepatitis is a rare complication after intravesical BCG instillation and only 5 cases have been reported. Its cause is unknown although it tends to be considered as a hypersensitivity reaction.44 The development of a granulomatous renal mass after intravesical BCG instillation is another potentially serious effect that occurs in 0.1% of patients and the action mechanism is principally through vesicoureteral reflux or systemic implants.45 Aortic aneurism infection secondary to intravesical BCG administration is extremely rare and is a potentially fatal complication of this immunotherapy in patients with bladder cancer.46

Interstitial pneumonitis is a complication secondary to intravesical BCG therapy and has been observed in 0.7% of patients undergoing this treatment.47 Seven cases of osteomyelitis from BCG following intravesical application have been reported in the English-language literature.48

In the presence of alarming symptoms (high fever with chills and general malaise), reducing BCG dose by one half and administering 300 mg of isoniazid (INH) the day before and continuing for 3 days, with each instillation. Non-steroid anti-inflammatory and anticholinergic agents are usually useful in the treatment of these patients. It should be underlined that antituberculosis treatment does not seem to interfere with the antitumor effect of BCG. When secondary effects are serious it is recommendable to suspend BCG treatment and establish a triple antituberculosis therapy during a period of 3-6 months (INH 300 mg daily, rifampin 600 mg daily, ethambutol 1200 mg daily). If sepsis is diagnosed it is preferable to use 250-500 mg cycloserine twice a day as shock treatment until the patient is stabilized in 3-7 days since this drug can inhibit bacilli growth in 24 hours.45,49

■ CONCLUSIONS

Superficial bladder carcinoma is a frequent disease with uncertain biological behavior. Initial treatment of this type of tumor is transurethral resection of the visible tumor. BCG vaccine application has been shown to be efficacious adjuvant treatment in bladder tumor management at this clinical stage. Complete response levels have been reached with this treatment that in some cases have been comparable to response levels in intracavitary chemotherapy and in other cases have been better. BCG therapy-related recurrence and progression times of tumors in this clinical stage are better than those obtained with transurethral resection alone or compared with other chemotherapeutic agents. A dose of 120 mg has been shown to be the most effective in aggressive tumor treatment including Tis. A weekly induction regimen for six weeks followed by another maintenance regimen every three weeks for three months and then every six months for three years maintains adequate antitumor response in the patient receiving vaccine instillation. Toxicity resulting from repeat BCG regimens has motivated the search for lower doses with the same effectiveness.

BIBLIOGRAFÍA

Bacillus Calmette-Guérin immunotherapy in the treatment of superficial bladder cancer


