BCG Immunotherapy for Transitional-Cell Carcinoma in Situ of the Bladder

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Prior to the advent of BCG immunotherapy, bladder carcinoma in situ often progressed to muscle invasion. Intravesical chemotherapy completely eradicates the disease in 50% of patients, but fewer than 20% remain disease free after 5 years. Complete responses have been reported in 70% or more of BCG treated patients, nearly two-thirds of which are durable.

Introduction

Unlike in situ carcinomas of other organs, transitional-cell carcinoma in situ (CIS) of the bladder is a highly aggressive, potentially life-threatening malignancy. The recognized lethality of CIS, and the general ineffectiveness of such treatment options as transurethral fulguration, radiation therapy, and intravesical chemotherapy, led to the use of radical cystectomy as the treatment of choice.

In 1990, based on a Southwest Oncology Group (SWOG) comparison of TheraCys (Connaught) bacillus Calmette-Guérin (BCG) vs doxorubicin chemotherapy and six studies of Tice (Organon) BCG, the FDA approved BCG for the treatment of CIS. Continued experience confirms that intravesical BCG immunotherapy is now the initial treatment of choice for patients with CIS and that cystectomy can be safely reserved for the minority of patients who fail to respond completely to intravesical therapy. This review will summarize BCG immunotherapy for CIS, specifically discussing treatment techniques, results, adverse reactions, and alternative immunotherapeutic strategies. As background to this discussion, a brief overview of transitional-cell CIS will be provided.

Carcinoma in Situ of the Bladder

Carcinoma in situ of the bladder was first described in 1952 by Melicow [1]. The diffuse nature of CIS was demonstrated in a subsequent report of 30 cases in which CIS extended from the renal pelvis to the penile urethra [2]. Carcinoma in situ may occur as a primary disease, in association with papillary or solid tumors, or following tumor resection.

Irritative symptoms are common in patients with primary or concurrent CIS [3]. Hematuria also is a frequent presenting feature. Urinary cytology is positive in more than 90% of patients with CIS and is an important diagnostic procedure because cystoscopic findings and even bladder biopsy may be falsely negative.

Clinical Course

The clinical course of CIS is highly variable, but overall, prior to the advent of BCG immunotherapy, 54% of patients progressed to muscle-invasive disease [4]. Extensive, diffuse disease is considered to pose an increased risk for progression, whereas focal disease may exist for years and has a reported incidence of progression as low as 8% [5].

Focal CIS is the earliest stage in the evolution of invasive bladder cancer, and although its course is often protracted, regression virtually never occurs. Patients with focal disease are optimal candidates for intravesical therapy.

Diffuse, widespread disease is typically associated with irritative symptoms, and up to 34% of patients treated with cystectomy will be found to have unsuspected microinvasive carcinoma [6]. In situ disease extends to the distal ureter in as many as 57% of patients and to the prostatic urethra in as many as 62% [6]. Despite cystectomy, death from metastatic disease occurs in up to 6% of high-risk CIS patients.

Radiation and Systemic Chemotherapy

The results of radiation therapy for CIS are disappointing. In a series of 11 patients treated with external-beam radiation therapy, 10 (91%) died at a mean follow-up of 3.5 years [5]. Similarly, although systemic chemotherapy may temporarily eradicate CIS, local recurrence is a virtual certainty.
Intravesical Chemotherapy
The results of topical intravesical chemotherapy have been much more encouraging, and this
treatment modality continues to have a role in the management of CIS. In a review of 448 patients
-treated with intravesical chemotherapy, the overall complete response rate averaged 48%.
Complete responses were reported in 38% of 89 patients treated with thiotepa (Thiotepa), 48% of
212 patients treated with doxorubicin, and 53% of 147 patients treated with mitomycin (Mutamycin)
[4].
In most series, fewer than 20% of patients treated with intravesical chemotherapy remain disease
free for 5 years or more, but preliminary encouraging results have been reported with the
combination of mitomycin and doxorubicin followed by maintenance chemotherapy [7]. In the
absence of a clear indication for intravesical chemotherapy (ie, suspected or confirmed residual
disease), unnecessary instillations should be avoided, as repeated instillation of thiotepa,
doxorubicin, or mitomycin in normal rodent bladders reportedly induces atypia, CIS, and even
invasive transitional-cell carcinoma [8].

BCG Immunotherapy
Bacillus Calmette-Guérin, a live attenuated Mycobacterium bovis vaccine, was first reported to have
antineoplastic activity in 1935 by Holmgren [9]. However, it was not until 1976 when Morales et al
first reported the use of intravesical BCG in the management of early-stage bladder cancer [10].
Since then, many studies have confirmed the efficacy of intravesical BCG in the treatment of
superficial bladder cancer and CIS (see Table 1).

Antineoplastic Mechanism
Bacillus Calmette-Guérin is a nonspecific immune stimulant. Intravesical instillation of BCG induces
an inflammatory cell infiltration with a broad range of cell types. Bacillus Calmette-Guérin activates
macrophages, T-lymphocytes, B-lymphocytes, natural killer cells, and killer cells [11]. It is known to
stimulate lymphokine and interferon production. This, in turn, is thought to enhance natural killer cell
activity, an increase of which has been observed after BCG immunotherapy [12-14]. Bacillus
Calmette-Guérin produces a T-cell-mediated response linked to antitumor activity in both humans
and mice [15]. Bohle et al have demonstrated that in addition to the typical lymphokine-activated
cell activity induced by interleukin-2, BCG appears to induce an entirely new variety of killer cells termed “BCG-activated killer” (BAK) cells [16]. The antineoplastic effect of BCG appears to
result from enhanced activity of various arms of the immune system.
The mechanism of BCG-tumor cell interaction is not yet well understood but may be critical to the
effective eradication of tumor cells. After intravesical instillation, live mycobacteria attach to the
urothelial lining, facilitated by fibronectin (a component of the extracellular matrix) and then are
internalized by bladder epithelial cells [17,18]. This process leaves bacterial cell surface
glycoproteins attached to epithelial cell membranes, and these antigens are thought to mediate the
immune response [19]. Tumor cell motility is also thought to be inhibited by BCG through a
mechanism involving the BCG-fibronectin-tumor cell interaction [20].

Efficacy
At present, BCG is the most effective intravesical agent known for the prevention of recurrence and
progression of bladder cancer [21]. Multiple studies have established that BCG prophylaxis following
complete transurethral resection (TUR) or fulguration of superficial disease significantly reduces
recurrence and prolongs disease-free interval in comparison to TUR alone. Of five controlled studies
of BCG prophylaxis encompassing a total of 496 patients, four demonstrated a significant reduction in
tumor recurrence; overall, the rate of tumor recurrence with intravesical BCG was 32%, as
compared with 72% for surgery alone-a 40% reduction ($P < 0.0001$) [22].

Effect on Tumor Progression--The effect of BCG on tumor progression has been investigated in
three randomized studies involving 335 patients. Herr et al found that BCG significantly prolonged
the time to progression to muscle invasion or metastasis in 86 patients [23]. Mortality was reduced from
32% to 14% with BCG despite the more frequent (42% vs 26%) and earlier (mean, 11 vs 36
months) use of cystectomy in the control group. In a subsequent report on the same patients after
an additional 3 years of follow-up, cancer deaths were reduced from 37% to 12% ($P < 0.01$) [24].
The SWOG found that stage or extent of disease increased in 37% of patients receiving doxorubicin,
as compared with 15% of those receiving BCG [25]. In a randomized study of 133 patients with
superficial bladder cancer conducted by Pagano et al, progression to stage T2 or higher occurred in
17% of control patients vs 4% of those treated with BCG [26]. Each of these studies found a
significant reduction in disease progression with the use of intravesical BCG; the mean rate of
progression was 28% for controls vs 14% for those receiving BCG. Bacillus Calmette-Guérin has proved highly successful in treating CIS. A review of 34 series involving 1,354 patients shows an average complete response rate of 72% (see Table 1). Responses are seen with all preparations studied, and range from 39% to 100%. The SWOG study of 64 CIS patients treated with BCG had a complete response rate of 70% and a median duration of response of 39 months. In this study the first treatment began 1 week after tumor resection, and was followed by five weekly treatments, for a total of six treatments. Additional treatments were administered 3, 6, 12, 18, and 24 months after resection. In a second SWOG study in which patients received an additional 3-week course of BCG at 3 months, the overall complete response rate rose to 87%. Maintenance BCG therapy consisting of three weekly treatments every 6 months for 3 years has yielded an estimated 4-year disease-free rate of 83%.

In summary, BCG has supplanted cystectomy as an initial therapy for CIS. It remains to be shown whether initial cystectomy is superior to an initial trial of BCG followed by cystectomy in those who fail to respond completely.

**Principles Of BCG Immunotherapy**

Animal studies and subsequent extensive clinical experience have elucidated several factors of importance in optimizing the response to BCG immunotherapy:

**Tumor Burden**—Animal studies have demonstrated that the antitumor response to BCG is limited by tumor burden [27], and therefore, all visible tumor should be resected or fulgurated prior to initiation of BCG treatment.

**Lowest Effective Dose**—Also, optimal response requires a sufficient number of viable organisms and direct juxtaposition of BCG and tumor cells. Although a sufficient number of colony-forming units is required for response, the dose-response curve for BCG immunotherapy, like most biologic-response modifiers, is bell shaped [28]. Dose reduction has clinical relevance because Morales et al have shown that it significantly decreases the toxicity of intravesical BCG [29]. Surprisingly, data collected by Pagano and associates have suggested that 75 mg of Pasteur BCG is not only less toxic but also more effective than the standard 150-mg dose [30]. In their randomized trial involving 183 evaluable patients, low-dose Pasteur BCG resulted in a 40% improvement in 5-year disease-free status when compared with standard-dose BCG. A multicenter protocol is currently underway in the United States and Canada to evaluate reduced-dose Connaught BCG.

**Optimal Duration of Therapy**—Importantly, immune stimulation and antitumor response in patients receiving intravesical BCG instillation appear to peak at the sixth weekly intravesical instillation. Continued administration after that time invokes suppressive immune responses and serves only to increase the toxicity of treatment for most patients. As might be expected, subsequent weekly instillations in patients who have already received an initial course of BCG results in peak immune stimulation at 3 weeks (L. deBoer, PhD, MD, personal communication, 1994). This observation is of particular importance when considering optimal maintenance schedules, as discussed below.

**Tumor Antigenicity**—Not all tumors are susceptible to immunotherapy. Whereas we once considered tumor antigenicity to be required, the observation that BCG can stimulate natural killer cells, interleukin-2, LAK cells, and distinctive BAK cells, which can nonspecifically kill malignant cells, suggests that tumor-specific antigenicity may not be required. Nevertheless, in both the murine bladder tumor model and patients, some transitional-cell carcinomas appear to be completely unresponsive to immunotherapy.

**Functional Immune System**—An intact immune system and, in particular, a functional T-cell immune system, is required for response to BCG immunotherapy. Individual components of the immune system can be blocked in animal models without eliminating the antitumor effect of BCG as long as the function of cytotoxic T-cells is preserved [15].

**BCG Treatment Techniques**

Experience with thousands of patients treated with BCG have confirmed that the basic principles of BCG immunotherapy demonstrated in animal models apply to the clinic. As mentioned above, optimal response to BCG requires the direct juxtaposition of sufficient numbers of viable organisms with tumor cells. Thus, BCG immunotherapy is remarkably effective in transitional-cell carcinoma of the prostatic urethra, producing a complete response rate similar to that reported in the bladder, but does not appear to reduce the occurrence of upper tract tumors. Although intravesical instillation results in contact of BCG with urethral tumors, in the absence of reflux, contact with upper tract
tumors does not occur. Optimal response occurs when tumor volume is minimized. While the 100,000-cell limit seen in mice fortunately does not apply to humans, every effort should be made to resect all visible tumor and fulgurate areas of CIS prior to initiation of BCG immunotherapy. Early treatment protocols attempted to instill BCG as soon as possible after tumor resection, but subsequent experience has shown that early administration increases the risk of intravascular dissemination of BCG. Therefore, BCG instillation is postponed for 1 to 2 weeks following transurethral bladder tumor resection.

Ratliff and associates demonstrated that fibronectin is an important attachment mechanism for BCG [31]. A retrospective review of patients treated with BCG at Washington University, St. Louis, showed a significant reduction of antitumor activity when BCG was given to patients taking clot inhibitors, including aspirin, dipyridamole, and warfarin [32]. A subsequent retrospective study from Australia confirmed these findings [33].

Optimal attachment of BCG occurs when BCG is diluted with preservative and bactericidal-free normal saline at pH 7.4. Attachment peaks 2 hours after instillation. As previously noted, with treatments repeated weekly, immune stimulation peaks at 6 weeks. It is remarkable that the treatment schedule found to be most effective resembles so closely the BCG regimen originally designed by Dr. Morales and colleagues [10].

**Induction Therapy**

Optimal BCG induction therapy appears to be six weekly BCG instillations followed by a 6-week rest period and an additional three weekly instillations. In the SWOG study of 218 randomized patients with CIS, six weekly instillations resulted in the expected 73% complete response rate [34]. With three additional treatments, the complete response rate increased to 87% (P < 0.04). Importantly, this "6 plus 3" schedule devised by the author should not be converted to a "9" schedule, as continued instillation beyond 6 weeks suppresses immune response and has resulted in a disappointing response rate.

**Maintenance Therapy**

Optimal maintenance therapy with BCG has now also been elucidated by SWOG studies [34]. In our early experience, a single instillation of BCG at 3-month intervals was associated with a fourfold reduction in the rate (not incidence) of tumor recurrence [35]. Two subsequent controlled trials failed to demonstrate that monthly [36] or quarterly [37] BCG maintenance therapy reduced the incidence of tumor recurrence.

In 270 patients with rapidly recurring, high-grade, or stage T1 superficial transitional-cell carcinoma, the results of maintenance BCG using three weekly instillations of 120-mg Connaught BCG was even more dramatic. Of patients randomized to a single 6-week BCG course, 50% remained disease free for 4 years or more. In patients who were disease free and were given maintenance therapy at 3 months, 6 months, and every 6 months thereafter up to 3 years, a 33% improvement in long-term disease-free status was observed; 83% of these patients were tumor free at 4 years (P < 0.000001). A similar benefit was seen in patients with CIS. Considering only those patients who were disease free at 3 months, continued three weekly maintenance BCG treatments increased long-term disease-free status from the expected 65% to 83% (P < 0.01). With 391 patients in this randomized trial evaluable for survival, maintenance BCG was found to improve 4-year survival from the expected 86% to 92% (P < 0.04) [34].

**Vitamin Supplementation**

Epidemiologic, in vitro, and animal model studies have suggested that various vitamins, including vitamins A, B6, C, and E, may have a protective or even therapeutic effect in many cancers, including bladder cancer. Immunotherapy can markedly alter vitamin metabolism. In patients given interleukin-2 immunotherapy, serum vitamin C levels were depressed to undetectable levels in 12 of 15 patients [38], and 60% of patients were found to be hypovitaminemic for vitamin A, 80% for beta-carotene, 90% for vitamin B6, and 45% for folate [39].

We evaluated long-term administration of recommended daily allowance (RDA) multivitamins alone vs RDA multivitamins plus high doses of vitamins A, B6, C, and E in 65 BCG-treated patients with superficial transitional-cell carcinoma, one-third of whom had CIS. In this randomized double-blind study, high-dose vitamin administration (Oncovite, Mission Pharmacal) was associated with a 40% long-term reduction in tumor recurrence (P < 0.02) [40]. While natural killer cell activity was not significantly elevated following BCG therapy in patients receiving RDA vitamins, it was significantly increased in those receiving high-dose vitamins [40].

These remarkable results, which exceed the benefit currently reported with intravesical chemotherapy in superficial bladder cancer, need to be independently evaluated, but I currently recommend high-dose vitamin supplementation for all my bladder cancer patients.
Complications of BCG Immunotherapy

The mechanism of action of BCG results in symptoms that previously were included in the list of adverse reactions to treatment and may have led to the erroneous conclusion that BCG is poorly tolerated. In fact, serious adverse reactions to BCG are rare, and 95% of patients tolerate BCG well [41].

Common Adverse Effects

Urinary frequency, mild dysuria, low-grade fever, and malaise lasting for up to 2 days and generally beginning after the third instillation are a consequence of the immune stimulation of BCG, and are associated with inflammatory cell infiltration of the bladder and cytokine and interferon release. These common symptoms respond well to symptomatic treatment with phenazopyridine, anticholinergics, antihistamines, and acetaminophen as needed.

When symptoms last more than 48 hours or do not respond to symptomatic medication, isoniazid (300 mg/d) can be given; this therapy typically resolves symptoms promptly. Isoniazid treatment is continued for several days after resolution of symptoms and can be reinitiated 1 day before subsequent BCG instillations and continued for 3 days.

Major Adverse Effects

Major adverse reactions to BCG are seen in less than 1% of patients but can be life threatening. High fever--Temperature elevations to 103°F or higher occur in 2.9% of patients treated with BCG immunotherapy [41]. This fever generally resolves spontaneously, but we recommend hospitalization and initiation of 300 mg of isoniazid and 600 mg of rifampin (Rifadin, Rimactane) daily because the innocuous febrile response cannot reliably be distinguished from the fever associated with the onset of BCG sepsis.

BCG sepsis has been reported to occur in up to 0.4% of patients, and 10 fatalities have been related at least temporally to BCG administration. Fortunately, despite a marked increase in BCG use, the incidence of septic reactions appears to have diminished now that the techniques to prevent, diag-nose and treat BCG sepsis have been emphasized.

Briefly, septic reactions most commonly occur when BCG is injected or absorbed into the bloodstream. Thus, BCG should not be instilled in patients who have experienced traumatic catheterization, with blood draining from the catheter. Similarly, in patients with persistent cystitis, BCG treatment should be delayed until symptoms resolve.

The diagnosis of BCG sepsis must be made on clinical grounds because treatment must be initiated promptly and cultures for the organism are commonly falsely negative. Patients should also be covered for the much more common gram-negative sepsis that occurs after urologic procedures, but in patients who have received BCG it must be assumed that BCG is responsible for the sepsis. Optimal survival in reported clinical cases and laboratory animal tests has been seen with the use of isoniazid (300 mg/d), rifampin (600 mg/d), and prednisolone (40 mg/d). Ethambutol (Myambutol) or cycloserine (Seromycin) can be also used. While cycloserine is more rapidly acting than the other antituberculous agents, we now reserve it for those few patients who fail to respond promptly to initial treatment.

Alternative Immunotherapies

The remarkable effectiveness of BCG immunotherapy in superficial bladder cancer suggests that other immunotherapeutic treatments may be highly successful. Several such treatments are proving to be effective, and there is optimism that these treatments may be less toxic as well as effective in patients who have failed to respond to BCG. While interferon-alpha, Keyhole Limpet hemocyanin (KLH), and bropirimine have demonstrated efficacy in superficial bladder cancer, to date none of these immunomodulators appears to achieve the level of success seen with current BCG treatment schedules.

Interferons

Interferons are remarkably nontoxic when given intravesically, and studies clearly show their efficacy in the treatment of superficial bladder cancer. Using leukocyte interferon-gamma intramuscularly, three small studies found responses ranging from a 43% partial response rate to a 75% complete response rate [42]. No response was seen when recombinant interferon-gamma-1B (Actimmune) was used, however [43].

The most encouraging results have been reported with intravesical interferon-alpha-2b (Intron A). In a dose-response study that tested intravesical interferon-alpha doses ranging from 50 million to 1,000 million units, Torti et al reported a 25% complete response rate in papillary tumors and a 32%
complete response in patients with CIS [44]. Remarkably, no significant toxicity was observed even at the highest dose.

In a subsequent multicenter randomized trial reported by Glashan [45], 100 million units of interferon-alpha given weekly for 12 weeks and then monthly to 1 year was found to be significantly better than 10 million units given on the same schedule. Complete biopsy and cytologic resolution of CIS occurred in 43% of patients randomized to 100 million units and only 5% of patients randomized to the lower dose. Importantly, complete response was observed in some patients who had not responded to a course of BCG immunotherapy, and many of the responses were of long duration. While this study confirms the efficacy of interferon in the treatment of transitional-cell carcinoma and demonstrates that 100 million units is superior to 10 million units, one should not conclude that the 100-million unit dose or the schedule employed is optimal. As noted above, the dose-response curve of biologic-response modifiers is typically bell shaped. Our group and other researchers have observed excellent responses with 50- to 60-million unit doses, and we are currently using the three-weekly, 6-month maintenance schedule found to significantly improve the results of BCG immunotherapy.

Continued research will be required to define the optimal treatment schedule for interferon and its ideal role in the management of superficial bladder cancer. Initial randomized comparison studies with BCG immunotherapy have confirmed that interferon is substantially less toxic but also less effective than BCG. In a study reported by Kalble et al, disease recurred in 5 (16%) of 32 patients with superficial bladder cancer treated with BCG, as compared with 21 (60%) of 35 patients given interferon-alpha ($P = 0.003$) [46].

**Keyhole Limpet Hemocyanin**

Keyhole Limpet hemocyanin is a highly antigenic complex glycoprotein with a molecular weight of 8-million Da that serves as the oxygen-carrying molecule for the mollusk *Megathura crenulata*. Olsson et al originally used 5-mg intradermal inoculations of KLH to correlate immune competence with reduced risk for tumor recurrence in patients with superficial bladder cancer [47]. Remarkably, patients who received intradermal KLH showed a dramatic reduction in tumor recurrence. In a subsequent prospective trial, these researchers found KLH immunization to significantly reduce tumor recurrence. In 1988, Jurincic et al reported the results of a randomized comparison of 10- mg intravesical KLH and mitomycin [48]. Tumor recurrence was reduced from 39% in the mitomycin group to 14% in the KLH group, and KLH was found to be essentially free of toxic reactions. A subsequent randomized clinical trial compared 30 mg of intravesical KLH with ethoglucid (Epodyl) in patients with superficial bladder cancer [49]. Tumors recurred in 55% of patients treated with KLH and 61% of those treated with ethoglucid.

Several animal model studies have confirmed that KLH has significant antitumor activity in bladder cancer. An ongoing phase I/II clinical trial has found that KLH produces complete responses in the range of 50% with virtually no toxicity.

**Bropirimine**

Bropirimine is an orally active pyrimidinone that has a wide variety of immunostimulatory activities, including the induction of interferon and other lymphokines, enhancement of natural killer cell activity and macrophage cytotoxicity, and heightening of antibody production [50]. Bropirimine is excreted in the urine in active form, and initial animal studies in transitional-cell carcinoma demonstrated marked inhibitory activity [51]. In a phase I trial involving 34 patients with papillary or in situ transitional-cell carcinoma of the bladder, 6 of 26 evaluable patients had a complete response to oral bropirimine. In a subsequent multicenter evaluation of bropirimine in 54 patients with CIS, 27 of whom had failed to respond to prior BCG therapy, a complete response was seen in 50% of patients. These data suggest that bropirimine will have a future role in the management of transitional-cell carcinoma. An important future application for bropirimine may be the treatment or prophylaxis of transitional-cell carcinoma of the upper urinary tract. While BCG immunotherapy is effective when directly applied to upper tract tumors, the oral route of administration is far more convenient and should be associated with less morbidity.

**Conclusions**

Bacillus Calmette-Guérin treatment of CIS of the bladder represents the most successful application of immunotherapy to human malignancy. In contrast to historical series, in which 54% of patients with CIS progressed to muscle-invasive disease and complete response to surgical fulguration or
intravesical chemotherapy occurred in a minority of patients, current optimal BCG induction therapy produces complete responses in 87% of patients. Moreover, with maintenance therapy using three weekly instillations every 6 months, 83% of complete responses are 3 years in duration. Patients treated with BCG remain at risk for extravesical recurrence of CIS, particularly in the distal ureters, and close surveillance is essential. With meticulous follow-up, however, most patients can be safely spared the trauma of radical cystectomy unless they do not respond completely or become resistant to treatment. Patients with focal recurrence may also respond to intravesical chemotherapy or alternative immunotherapies, and these individuals are important resources for the development of improved treatment alternatives for future patients.

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