Education Initiative in Urology

THE TREATMENT Tx REPORTER℠ UROLOGY

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FAQs on Intravesical Immunotherapy for Superficial Bladder Cancer

VOLUME II • PART 3

Personal insights from Dr. Michael A. O'Donnell, principal investigator of BCG/interferon trials

Dear Colleague:

Intravesical immunotherapy with bacillus Calmette-Guérin (BCG), alone or in combination with interferon, provides the best risk:benefit ratio for adjuvant treatment of moderate- and high-risk superficial bladder cancer following transurethral resection. Nonetheless, BCG is associated with potential local and systemic toxicity, so it is important for physicians using it to be familiar with the prevention and treatment of BCG-related complications.

Following recommended guidelines for dosing and administration, as discussed in Part 2 of this *Tx Reporter* series, will go a long way toward prevention of BCG side effects. Here in Part 3 of the series, I address questions regarding treatment of common and serious side effects once they have occurred, not only for BCG but for interferon as well. This issue addresses use of symptomatic therapies, the need to avoid specific prophylactic antibiotics, recognition of allergic reactions, emergency treatment of BCG sepsis, and how to determine the need for treatment discontinuation. As in the rest of this unique *Tx Reporter* series, these represent actual questions that I have received from colleagues like you. I hope that you find this newsletter useful in your clinical practice.

Sincerely,

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Now available at www.projectsinknowledge.com:

Part 1:	Current data on BCG/interferon combination therapy and their implications, including its relative benefits over BCG alone, its placement in current treatment algorithms, and the selection of appropriate treatment candidates
Part 2:	The recommended protocol for dosing and administration for BCG-naive patients and those with a prior history of BCG/interferon therapy. Includes protocols for induction, reinduction, and maintenance therapy, as well as dose reductions for side effects

Coming soon:

Part 4:	Diagnosis and treatment of recurrence in patients who have already received one course of treatment with immunotherapy

Inside This Tx REPORTER℠

Did You Know?

- BCG has been used in the treatment of bladder cancer for more than 20 years.
- Response to BCG is associated with a high urinary T helper 1 lymphocyte cytokine profile, which may take repeated BCG administrations to mount; this supports the practice of BCG reinduction therapy.
- Overexpression of COX-2 has been identified in both in situ and invasive transitional cell bladder cancers, leading to current investigations of COX-2 inhibitors in treatment and prevention of recurrence.
- Megadoses of vitamins reduce 5-year recurrence rates by 40% among patients treated with BCG.
- BCG may cause tuberculin sensitivity, so tuberculin reactivity PPD tests should be conducted prior to BCG therapy.

Sources: Bassi P. *Surg Oncol.* 2002;11:77.
Saint F, et al. *J Urol.* 2001;166:2142.
www.medscape.com/viewprogram/172.
Lamm DL, et al. *J Urol.* 1994;151:21.

Learning Objectives

This educational activity is designed to update urologists on the latest developments in the use of intravesical immunotherapy for treatment of superficial bladder cancer.

After participating in this activity, physicians will be better able to:

- **Consider the latest data regarding BCG/interferon combination therapy when formulating treatment plans for patients with superficial bladder cancer**
- **Select appropriate candidates for BCG/interferon combination therapy and BCG monotherapy**
- **Formulate a treatment plan using immunotherapy that includes appropriate doses and treatment intervals**
- **Prevent and manage toxicities associated with BCG and interferon**
- **Diagnose and treat recurrences of superficial bladder cancer following an initial course of immunotherapy**

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Introduction

Prevention and management of side effects are key components of care for patients receiving intravesical immunotherapy for treatment of superficial bladder cancer. Instillation of BCG into the bladder at full dose is associated with cystitis (91%), hematuria (43%), low-grade fever (29%), and malaise (24%). In general, these side effects can be managed symptomatically and usually clear within 12 to 24 hours. Other, more serious adverse events include high uncontrollable fever, granulomatous prostatitis, and major hematuria, which are less common but may be dose limiting. BCG is contraindicated in patients who are immunosuppressed or have active tuberculosis.

BCG/interferon combination therapy was found to be associated with an "acceptable level of serious toxicity" compared with what has historically been observed with BCG monotherapy in a recent analysis of toxicity among 1100 patients treated in a national multicenter phase II trial of BCG/interferon (Table 1), which is being overseen by Dr. O'Donnell. Ten cardiac events (ischemia, congestive heart failure, and arrhythmia) occurred in patients treated with BCG/interferon in this study, eight of which were thought to be unrelated to treatment. There were also six reversible neurologic events (confusion, transient ischemic attack, cerebrovascular accident, and weakness) and four miscellaneous events (vitiligo, conjunctivitis, metallic taste, and elevated liver function test values). No substantial increase in severe toxicity was seen among patients who had previously been treated with BCG monotherapy compared with BCG-naive patients. In the remainder of this *Tx Reporter,* Dr. O'Donnell addresses questions regarding the safety of BCG/interferon and strategies for preventing and managing its side effects.

Q. After a third dose of BCG/interferon induction therapy, one of my patients experienced severe urinary urgency and frequency, and continuous pelvic pressure. I started isoniazid, and when she had not improved after about 1 week, I added rifampin and ciprofloxacin. It has been about 3 weeks, and her symptoms persist. Urinalysis is normal. She has not been febrile and is otherwise well. Are these symptoms related to treatment?

Dr. O'Donnell: Your patient appears to have developed "BCG cystitis," which is a treatable side effect of BCG. I personally have treated over a half-

Table 1. BCG/Interferon: Serious Adverse Events.

	BCG/Interferon (n = 1100)*	BCG (n = 2606)†
Fever	2.9%	2.9%
Prostatitis/epididymitis	0.4%	1.3%
BCG-osis/itis‡	0.9%	0.7%
Arthralgia/arthritis	0.4%	0.5%
Severe hematuria	0.7%	1.0%
Rash	0.3%	0.3%
Contracted bladder	0.2%	0.2%
Renal abscess	0.1%	0.1%
Sepsis	0.1%	0.4%

*National multicenter phase II study by O'Donnell et al. 2002. †Summary report of BCG monotherapy (Lamm, et al. *Prog Clin Biol Res.* 1989;310:335-355.) ‡Defined as recurrent fevers or BCG organ-associated infection without the acute hemodynamic changes seen with BCG sepsis.

O'Donnell MA, Hartman K, National Phase II BCG IFN-Alpha Investigator Group. An evaluation of BCG plus interferon-alpha-2b toxicity in a national multicenter phase II trial [abstract 760]. Presented at: 97th Annual Meeting of the American Urological Association; May 25–30, 2002; Orlando, Fla. Adapted by permission of the American Urological Association, with updates by Dr. O'Donnell.

dozen patients with this problem. While both isoniazid and rifampin are appropriate BCG-specific antibiotics, their onset of action is very slow, and they do not directly affect inflammation. Adding a fluoroquinolone such as ciprofloxacin was a good idea, since it is a fast-acting antibiotic, is very effective against BCG, and builds up in high concentrations in the urine. Unfortunately, inflammation may persist even after eliminating any residual living BCG. At this point, I would initiate prednisone at a dose of 40 mg once daily in the morning for 3 days. Thereafter, you should decrease the dose by half every 3 days, until discontinuing prednisone after day 15. If necessary, the taper can be extended or drawn out more slowly over a 3- to 4-week period, but I have found that most patients begin to respond within a few days and are able to stop prednisone completely within 2 to 3 weeks. Not all symptoms will resolve completely, but these approaches should break the cycle and allow more gradual resolution of symptoms. Please note, *it is very important that the antituberculosis antibiotics (at least ciprofloxacin or isoniazid) be continued throughout the prednisone therapy and for at least 2 weeks thereafter,* because prednisone can weaken the immune system, allowing any live BCG to multiply.

In addition, it may be helpful to add one of the newer COX-2 anti-inflammatory drugs such as rofecoxib 25 to 50 mg/d during treatment with prednisone and continuing (if needed) for the next 2 to 4 weeks. Rofecoxib is well tolerated, does not cause stomach upset, and does not thin the blood. It should not be given in conjunction with aspirin or other nonsteroidal anti-inflammatory agents.

I am generally reluctant to re-treat patients with BCG if they have developed BCG cystitis. If you must re-treat, I would recommend waiting at least 6 months after all inflammation has resolved, and then using a very low dose of BCG (eg, 1/30 or 1/100) with 100 mIU interferon. For future reference, to prevent this condition in other patients, you should defer treatment if symptoms from the prior weekly administration have not resolved within 3 to 5 days or if the *unspun* urinary white blood cell (WBC) count per high-power field (hpf) is >5 (which corresponds to approximately 100 WBC/hpf for spun urine). It is acceptable to delay treatment by 1 to 2 weeks and/or to reduce the BCG dose to a third of the previously used dose, and even to omit the final maintenance treatment in any given cycle, for patients with more severe local reactions, in order to avoid precipitating this condition.

Q. A patient has developed a pruritic, papular erythematous rash after a couple of doses of BCG/interferon. Is this a side effect of treatment, and how should it be managed?

Dr. O'Donnell: Unfortunately, the rash represents an allergic reaction to BCG and/or interferon, which occurs in approximately three out of every 1000 patients treated with either BCG monotherapy or BCG/interferon combination therapy. The necessity for treatment discontinuation depends on the severity of the rash. I favor continuing treatment for mild rash, which may respond to topical therapy (eg, hydrocortisone cream). If it recurs, or if the rash is more severe, treatment should be permanently discontinued. (Note that dose reduction does not help in cases of allergic reaction.) The rash should subside after stopping therapy.

Q. Should BCG/interferon be discontinued if the patient develops gross hematuria or microhematuria?

Dr. O'Donnell: BCG alone or in combination with interferon can cause sporadic gross hematuria or microhematuria. Microhematuria is not a contraindication to treatment. For gross hematuria, I would not treat with BCG (alone or with interferon) during active bleeding, but would wait until bleeding had stopped for at least 24 hours. If necessary, the BCG dose can be reduced to one third the previous dose, possibly even increasing the interferon dose to 100 mIU for very low-dose (1/30–1/100) BCG reductions.

Q. What is the recommended treatment for BCG sepsis, and after it is resolved, can I re-treat with BCG/interferon or should I use interferon alone?

Dr. O'Donnell: BCG sepsis is recognized as high fever/shaking chills together with hemodynamic collapse (hypotension). Patients with BCG sepsis should be treated immediately with intravenous fluid plus isoniazid 300 mg, rifampin 600 mg, ethambutol 1200 mg, and prednisolone 40 mg. Although older literature recommended cycloserine as first-line treatment for BCG sepsis based on theoretical concerns and use in tuberculosis, recent testing of BCG has shown it to be resistant to cycloserine. In cases of severe complications, or if one of the standard antituberculosis drugs is not tolerated, or if coincident gram-negative sepsis is a concern, fluoroquinolones should be added to the regimen.

No further BCG should be given, even after resolution of sepsis. As an alternative treatment, consider interferon monotherapy, which is associated with response rates of 25% to 75% in patients with residual papillary transitional cell carcinoma and 66% in patients with carcinoma in situ. The recommended dose would be 100 mIU in 50 cc normal saline QW for a total of 6 to 8 weeks. Monthly maintenance has been recommended, but its efficacy has never been confirmed.

Q. What prophylactic antibiotics can be used in a patient receiving BCG/interferon?

Dr. O'Donnell: If medically indicated, penicillins or amoxicillin/clavulanate, cephalosporins, nitrofurantoin macrocrystals, ampicillin, trimethoprim/sulfamethoxazole, or vancomycin can be used safely in patients receiving treatment with BCG/interferon.

Fluoroquinolones, macrolides, tetracyclines, and aminoglycosides should *not* be used in conjunction with BCG instillation, since they potentially render the BCG nonviable and ineffective.

Q. A patient who recently completed induction therapy with BCG/interferon has elevated and increasing liver enzyme levels, which were normal at baseline. Cystology and cytology are normal. Are the liver enzyme elevations attributable to interferon?

Dr. O'Donnell: Interferon is prescribed as treatment for viral hepatitis and usually helps improve liver enzyme levels in these patients; however, flare of liver enzyme levels has been reported in some hepatitis C patients with normal enzyme levels at baseline. It is not clear, however, that this occurs with intravesical therapy. We have had only one other patient who developed elevated liver function tests during the first dose of induction therapy, and we were not certain whether these elevations had actually preceded therapy. In this case, the liver enzyme levels gradually returned to normal and did not increase again during the maintenance phase of treatment. There is a theoretical possibility that a patient may develop BCG hepatitis, in which case a CT scan should show granulomas. If the elevations persist after all other causes have been ruled out, it would be best to forgo BCG/interferon maintenance therapy and just continue to monitor the patient with cystoscopy and cytology.

Q. Does a male patient receiving treatment with BCG need to use condoms during sexual intercourse if his sole sexual partner is postmenopausal?

Dr. O'Donnell: Yes. Condoms are recommended not only for contraception but also to decrease the theoretical risk of BCG infection of the partner. BCG is shed from the urethra for at least 48 hours and for up to 1 week after treatment.

Q. The day before the sixth dose of induction therapy, a patient was hospitalized for a myocardial infarction. Should he continue BCG/interferon?

Dr. O'Donnell: I would recommend stopping treatment and continuing to follow the patient with cystoscopy and other routine monitoring. During our 1100-patient study using combination therapy, we saw three cases of cardiac events that occurred close enough to the time of therapy to suggest a causal relationship. Many of these patients have underlying cardiac disease due to smoking and advanced age. The occasional fevers invoked by immunotherapy could potentially add stress to the heart. Anyone with marginal cardiac status should be medically evaluated prior to starting intravesical immunotherapy.

Q. A patient developed swelling, itching, and tingling of his hands, and a swollen and tingling lip 3 days after treatment with full-dose BCG and interferon. The symptoms resolved and then returned spontaneously over the next couple of days. Is this a delayed reaction to treatment?

Dr. O'Donnell: This may be an allergic reaction to BCG or interferon. I would try treating the patient with 1/3-dose BCG alone next. If the symptoms do not recur, then premedicate the patient with diphenhydramine 50 mg before trying 1/3-dose BCG plus 10 mIU interferon. If the reaction occurs, then an interferon allergy should be assumed, and no further treatment with interferon should be given. If no reaction occurs, then the patient can continue on the reduced dose of BCG with 10 mIU interferon.

Q. I have a patient whose voiding cystogram shows right ureteral vesicle reflux up to the mid to distal ureter. Otherwise, cystourethrogram is negative. No focal bladder lesion is evident. Can I treat this patient with BCG/interferon or should I use interferon alone? Is there an increased risk of BCG-related toxicity due to the reflux?

Dr. O'Donnell: A German study by Dr. Bohle showed that vesicorenal reflux is not associated with an increase in BCG-related side effects or risk of complications. Thus, treatment with BCG with or without interferon would be an appropriate choice for this patient. TX

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