Education Initiative in Urology

THE TREATMENT Tx REPORTER℠ UROLOGY

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FAQs on Intravesical Immunotherapy for Superficial Bladder Cancer

VOLUME II • PART 2

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

Dear Colleague:

I am pleased to bring you the second in this four-part *Tx Reporter* series on intravesical immunotherapy in superficial bladder cancer. In Part 1, which is now available at www.projectsinknowledge.com, I discussed recent data on bacillus Calmette-Guérin (BCG) and interferon combination therapy and their important applications for clinical practice today. Here in Part 2, I am excited to share with you the specific details of the dosing and administration protocol I have developed for BCG/interferon, and to address some of the most commonly asked questions about this protocol.

As BCG/interferon is increasingly used in clinical practice for off-label treatment of superficial bladder cancer, it is particularly important for urologists to have clear recommendations regarding appropriate dosing and administration. This is especially true since dosing must vary according to the patient's past exposure/sensitization to and toleration of BCG, as well as with response to the initial induction regimen. The protocol I describe in this newsletter is based on clinical data from various studies of BCG and my own research with BCG/interferon. I personally have used it in treating more than 100 patients, and it is currently being evaluated in 1100 patients at 125 sites throughout the United States, in a study under my direction. I am excited about this opportunity to share this information with you and to address some of the actual questions that I recently received from colleagues like yourselves regarding this regimen. I hope that you find this issue, and the entire series, helpful and informative.

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

Coming Soon:

Part 3: Safety issues and side effects management, including management of BCG cystitis, rash, hematuria, BCG sepsis, and other side effects

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?

- Cigarette smoking accounts for up to half of all bladder cancer cases.
- Although men have a higher overall risk of bladder cancer than women, the impact of cigarette smoking on bladder cancer risk is greater in women than in men. Women who smoke >40 cigarettes/d for >40 years incur more than 11 times the risk of bladder cancer of nonsmokers, while men with similar smoking habits have approximately 5 times the risk of nonsmokers.
- Residence in the Northeast United States is associated with higher risk of bladder cancer compared with residence in the West, a difference not explained by smoking, diet, or other lifestyle factors.
- Caucasions develop bladder cancer twice as often as African Americans and Hispanics; Asians have the lowest rates.

Sources: Amling CL. *Curr Probl Cancer.* 2001;25:219. Castelao JE, et al. *J Natl Cancer Inst.* 2001;93:538. Michaud DS, et al. *Epidemiology.* 2001;12:719. www.cancer.gov. www.oncolink.com.

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

CME Information

Projects In Knowledge is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Estimated time for completion of this four-part activity: 1 hour. Projects In Knowledge designates this four-part educational activity for up to 1 hour in Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours that he/she actually spent in the educational activity.

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This activity may include a discussion of therapies that are unapproved for use or investigational, ongoing research, or preliminary data.

The opinions expressed during this activity are those of the faculty and do not necessarily reflect those of the sponsor or the commercial supporter.

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Introduction

Until optimal dosing and scheduling of BCG and BCG/interferon immunotherapy for superficial bladder cancer have been determined in prospective studies, clinical practice should be based on the protocols used in clinical trials in which these regimens showed clinical benefit. For example, BCG maintenance schedules vary from one investigation to another, but since an investigation by the Southwest Oncology Group (SWOG) showed the best evidence in favor of maintenance therapy, the schedule from the SWOG study is the one that is generally recommended. Studies have also supported the strategy of using reduced doses of BCG to improve tolerability without loss of efficacy, particularly in BCG-sensitized patients. Dosing for BCG/interferon combination therapy can be somewhat complex, since it is individualized according to whether the patient was previously treated with BCG and has a history of BCG-related side effects. Different doses are also used for induction, reinduction, and maintenance therapy, and doses may be reduced or delayed for patients with side effects. Table 1 illustrates the doses and schedule used by Dr. O'Donnell and colleagues in studies of BCG/interferon combination therapy. In this *Tx Reporter*, Dr. O'Donnell answers questions about this protocol, as well as about the measures and precautions needed to administer BCG safely and effectively and about the appropriate timing and type of monitoring to be performed during the treatment period.

Q. Why is a lower dose of BCG used for retreatment of patients with a prior BCG failure than for BCG-naive patients, and for reinduction compared with induction?

Dr. O'Donnell: Our data and those of several European studies show that after prior BCG exposure, high doses of BCG become immunosuppressive and are less effective with increasing degrees of BCG sensitization. Lower doses remain effective, even in sensitized patients. This is probably because the response to BCG follows a bell-shaped curve that shifts with prior sensitization.

Q. If a patient is BCG intolerant, are reduced doses of BCG as effective in combination with interferon?

Dr. O'Donnell: I generally recommend reducing the dose of BCG by 1/3

Table 1. BCG/Interferon Dosing and Administration Protocol.

	Schedule	Dose	
		for Prior BCG Failures	for BCG Naive
Induction therapy	QW x 6 wk*	1/3-dose BCG + 50 mIU IFN†‡	Full-dose BCG + 50 mIU IFN‡
Cystoscopy, biopsy, cytology	~6 wk after last induction dose	---	---
IF DISEASE-FREE AFTER INDUCTION:			
	Schedule	**Dose**	
Maintenance therapy	3 weekly miniseries: Series 1: 3 mo after end of induction Series 2 & 3: 6 and 12 mo later	Dose 1: 1/3-dose BCG + 50 mIU IFN‡ Doses 2 & 3: 1/10-dose BCG + 50 mIU IFN‡	
Cystoscopy	Every 3–4 months	---	
IF RECURRENT DISEASE AFTER INDUCTION:			
	Schedule	**Dose**	
Reinduction therapy	QW x 6 wk*	1/10-dose BCG + 100 mIU IFN‡	
Cystoscopy	~6 wk after last reinduction dose	---	
Maintenance therapy (only if disease free after reinduction)	3 weekly miniseries: Series 1: 3 mo after end of induction Series 2 & 3: 6 and 12 mo later	All 3 doses: 1/10-dose BCG + 50 mIU IFN‡	
Cystoscopy	Every 3–4 mo	---	

*8 weeks of induction therapy was given in the initial half of the study, but later administrations were associated with an increased rate of side effects without obvious additional clinical benefit. †1/3 of an 81-mg vial of Connaught strain BCG equal to 27 mg diluted in 50 cc buffered saline, in which 1 cc of freshly reconstituted 50 mIU interferon is added. ‡BCG dose may be reduced in gradations of 1/3 (to 1/10, 1/30, or 1/100) as necessary for treatment intolerance by reducing the amount of BCG concentrate delivered into the standard 50 cc buffered saline volume. IFN dose should be increased to 100 mIU. Treatment delays up to 2 weeks are also permitted.

increments. For any previously treated patient, I start with 1/3 of the standard dose in the same 50 cc volume of diluent. The easiest way to make the dose reduction is to simply add less of the BCG concentrate. For Tice®, the standard dose is 1 cc, so I add only 0.33 cc to the 50 mL final volume. Additional 1/3-dose reductions (to 1/10, 1/30, and 1/100 the standard dose) and 1- to 2-week delays are recommended in the case of evolving BCG intolerance, primarily persistent cystitis. (I do not treat if they are still symptomatic from the prior dose.) These lower doses are tolerated by many patients previously considered BCG intolerant. If I reduce the BCG to 1/10 during a 6-week induction or reinduction, I increase the interferon dose to 100 mIU. By reducing symptoms to a tolerable level, patients are more likely to stay on therapy longer, and urinary immune responses (as measured by cytokine levels) are actually better. Another way to mitigate BCG intolerance is to premedicate with a nonsteroidal anti-inflammatory drug, preferably a COX-2 inhibitor, with or without an antispasmodic.

Q. Occasionally, patients want to change their treatment day (eg, a patient receiving treatment on Fridays does not want to come in the Friday after Thanksgiving). What is the minimum number of days between weekly doses?

Dr. O'Donnell: Doses should be spaced at least 6 days apart to avoid increased toxicity, but can be delayed to as late as 14 days as needed. Even a 3-week delay is occasionally permitted, though not encouraged. However, our data show that by 4 weeks, the benefit of the prior treatment is often lost. This is probably the reason why monthly maintenance therapy is unreliable.

Q. What is the optimal timing of cystoscopy during treatment?

Dr. O'Donnell: Cystoscopies should be performed every 3 to 4 months during the first 2 years after a transurethral resection of bladder tumor (TURBT). They should be staggered with the induction and maintenance cycles of BCG/interferon so that 4 to 6 weeks elapse after each treatment administration before the next cystoscopy is performed. This interval is necessary because BCG causes inflammation in the bladder that makes it hard to interpret cystoscopic findings, especially when carcinoma in situ (CIS; a red velvety lesion) is suspected. It is also necessary to allow sufficient time to elapse *after* cystoscopy before giving the next treatment. In fact, it is generally a bad idea to administer BCG within 10 to 14 days of *any* invasive procedure that may inadvertently cause bleeding, potentially providing a means by which BCG can get into the bloodstream. This is especially true if a TURBT or bladder biopsy has been performed, after which early administration of BCG has resulted in fatalities! If cystoscopy is performed without biopsy, then a 1-week delay before administering treatment would probably be appropriate. Although I avoid giving BCG on the same day as a cystoscopy because of the possibility of causing urethral trauma and bleeding, there are special circumstances in which this may be necessary (eg, after putting in a temporary external stent up to the ureter to provide upper-tract BCG instillations). With the proper staggering of appointments, the routine maintenance cycles are begun 4 to 6 weeks after the last surveillance cystoscopy, although they could be done sooner if needed.

Q. Should a biopsy be repeated at every cystoscopy during treatment?

Dr. O'Donnell: If the patient has a documented remission at the time of the first cystoscopy with biopsy, then I do not routinely biopsy again unless the cytology or cystoscopy is suspicious for recurrence. A biopsy could be omitted on the first cystoscopy if the original tumor was low grade, but I *always* biopsy at the first cystoscopy if there was prior CIS, stage T1 disease, any grade 3 disease, or any positive cytology.

Q. What other workup and evaluation are necessary before and during treatment?

Dr. O'Donnell: If the index cancer is stage T1, CIS, or grade 3/4, then upper tract imaging should be performed within 12 months. If the diagnosis of cancer is made on the basis of a positive cytology only (ie, no biopsy showing cancer), then an upper tract study should be done within 8 weeks of treatment initiation to be sure there is no cancer lurking in the kidney. Lower-grade papillary cancers without CIS may not require an upper tract study at all, although it is still good medical practice to perform one within 2 years. A recent cytology (within 8 weeks of treatment) is suggested, but not required, for grade 1 or 2 stage Ta papillary bladder cancer. It is *very strongly* suggested within 8 weeks of treatment, and at each subsequent evaluation cystoscopy, for any cancer with prior positive cytology, stage T1, prior grade 3/4, or prior CIS. These features define an aggressive subtype of bladder cancer.

Q. Does it matter whether the powder or the solution form of interferon is used?

Dr. O'Donnell: For BCG/interferon combination therapy, the powder formulation of interferon should be used. The solution should be avoided because it contains bacteriostatic preservatives that could kill the BCG and render it inactive, although this has not yet been confirmed. For interferon monotherapy, it does not matter which formulation of interferon is used.

Q. Are all strains of BCG the same?

Dr. O'Donnell: Although there are no data directly comparing the available strains of BCG, worldwide consensus is that most strains are essentially identical in terms of their intrinsic biologic activity. There may be important differences in processing and packaging, however, that affect stability in solution, shelf life, and total colony-forming unit count. At the standard starting dose these differences are likely inapparent, but as the doses are progressively reduced, differences may become more clinically relevant. The strain used in Pacis® (Armand-Frappier strain, substrain Montreal) is very closely related to the Connaught strain (Theracys®), and was the first strain used in early studies to prove that BCG was a successful agent for bladder cancer. We did test Tice® (developed from Pasteur strain) and Theracys in mixing experiments with interferon. Theracys outperformed Tice in the stability tests. After 2 hours of reconstitution, the viability of Tice began to drop rather precipitously,

whereas Theracys showed a slow steady rate of decline. During the first 2 hours, however, viability of both strains was fine. Thus, irrespective of the strain chosen, BCG should be administered immediately after reconstitution, and treatment completed within 2 hours. I have not yet performed tests specifically using Pacis. In my ongoing studies, sites are allowed to use any of the three commercially available and approved BCG products. So far, the clinical efficacy responses appear identical, but there may be differences in local side effects that we continue to study.

Q. Is it possible to instill the BCG first and then the interferon, rather than mixing them together?

Dr. O'Donnell: It is better to premix the two components. The two are completely biocompatible for at least 2 hours after physical mixing. With separate administration, there is a potential problem of leakage or failure to deliver the full amount of each drug. Also, the volume of 50 to 100 mIU interferon, once mixed, is only 1 to 2 cc, whereas that of the BCG is typically 50 cc.

Q. My current practice, after instilling intravesical immunotherapy, is to leave the drug in for 2 hours and have patients turn side to side and front to back every 15 minutes. This practice requires use of a considerable amount of space and nursing time. Are there any data to support its benefits?

Dr. O'Donnell: The common practice of rotating the patient is based purely on anecdotal experience, and there have been no studies suggesting that it is of any particular benefit. I have my patients ambulate right away and do not keep them in the clinic. I believe that walking around is just as good a way to slosh the medication around inside the bladder. On rare occasions when patients have primarily dome lesions, I do ask them to lie on their bellies for about 15 minutes after they get home.

Q. Can I use a smaller instillation volume (eg, 30 cc instead of 50 cc) for a patient with a small bladder capacity?

Dr. O'Donnell: It is certainly feasible to reduce the administered volume in a patient with low bladder capacity. I would not make up a higher concentration of BCG in the lower volume, but rather simply administer a proportionately smaller amount. However, the full interferon dose can be "concentrated" in the smaller volume. No one has formally tested this approach, but from a practical standpoint, there are some patients who do not retain all of the administered medication, either as a full volume or by length of time held in the bladder. We essentially have to accept whatever the patient is able to achieve.

Q. Is there a way to prevent BCG leakage during the 2-hour period that the patient is supposed to retain the drug?

Dr. O'Donnell: If a patient experiences this problem, then prior to the next BCG dose, have the patient chew one or two hyoscyamine tablets or dissolve the tablets by holding them under the tongue for about 30 minutes before the procedure. Hyoscyamine has a rapid onset but lasts for only 2 to 3 hours. If hyoscyamine is not available, then oxybutynin or tolterodine can be used, but must be taken 1 hour prior to the procedure since they take longer to work. If the patient still has trouble retaining the medication, then two oxycodone tablets 1 hour before the procedure usually work well.

Q. Does using a Uro-Jet® or any type of lubricating jelly decrease the efficacy of BCG or BCG/interferon?

Dr. O'Donnell: From a practical standpoint, in the United States, where the lubricating jellies are water-soluble, the answer is no. In contrast, the oil-based lubricants used in Europe can significantly diminish BCG viability. To minimize the *potential* effects of the Uro-Jet, I instruct patients *not* to empty their bladder completely before coming in. Once the catheter is inserted, I completely drain the bladder by aspirating back on the Foley using the "spent" Uro-Jet and then applying gentle Credé's pressure to get the bladder as empty as possible. This also effectively rids the bladder of residual lidocaine jelly. I have been using this technique for a number of years and it has worked very well. TX

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