Education Initiative in Urology

THE TREATMENT Tx REPORTER℠ UROLOGY

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FAQs on Intravesical Immunotherapy for Superficial Bladder Cancer

VOLUME II • PART 1

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

Dear Colleague:

I am thrilled to offer you this new and unique four-part *Tx Reporter* series that reflects my years of practice treating patients with bladder cancer. I have answered virtually hundreds of letters, e-mails, and phone calls from physicians like you and their patients who have had questions on bladder cancer treatment. Many of these questions have probed for answers to controversial issues or have touched on areas of care for which there are no simple and straightforward answers or guidelines. After reviewing some of these correspondences with Projects In Knowledge, we thought that offering an anthology of the most interesting, provocative, and clinically relevant questions with my answers could help you in your clinical practice.

The series focuses on my recent experience investigating bacillus Calmette-Guérin (BCG) and interferon combination therapy. Immunotherapy with intravesical BCG—the gold standard for treatment of superficial bladder cancer—is limited by its toxicity and by subsequent disease recurrence or progression in a disappointingly large number of patients. Improvements in treatment options that result in less toxicity, prevent or delay recurrence/progression, and avoid the need for cystectomy are needed. Recent evidence suggests that the combination of BCG plus interferon alfa-2b may be synergistic without increasing toxicity over BCG alone. Phase III trials are currently underway, but positive preliminary data regarding this combination have led to considerable interest in this regimen, as well as a number of questions regarding the interpretation of available data and the practical aspects of using BCG/interferon combination therapy. In this series of newsletters, I will address actual questions regarding BCG/interferon that I have received from colleagues like yourself. I hope you find this series helpful and informative.

Sincerely,

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Coming Soon—Parts 2, 3, & 4!

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Part 2:	The recommended protocol for dosing and administration of BCG/interferon 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
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?

- Bladder cancer is the fourth most common malignancy in men and the tenth most common in women
- In 2002, there will be an estimated 56,500 new cases and 12,600 deaths due to bladder cancer in the United States
- From date of diagnosis to date of death, bladder cancer is more expensive than colorectal, breast, prostate, or lung cancer

Sources: American Cancer Society. *Cancer Facts and Figures 2002.* SEER Cancer Statistics Review, 1973-1999. Available at: http://seer.cancer.gov/csr/1973_1999/. Riley GF, et al. *Med Care.* 1995;33:828–841.

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.

Disclosure Information

The Disclosure Policy of Projects In Knowledge requires that the faculty participating in a CME activity disclose to the audience any significant relationship they may have with a pharmaceutical or medical equipment company, product, or service that may be mentioned as part of their presentation, as well as any relationship with the commercial supporter of this 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

Intravesical immunotherapy with BCG and interferon alfa-2b combination therapy is emerging as an important strategy for treatment of superficial bladder cancer. Data from three clinical trials (see Table 1) suggest that BCG/interferon combination therapy may be superior to either agent alone and may allow reduction of BCG dose (and thus its toxicity) without compromising antitumor efficacy.

In the largest and most recent of these studies, O'Donnell et al treated 40 patients who had failed one or more courses of BCG therapy with BCG/interferon combination therapy. Treatment consisted of 1/3-dose BCG plus 50 mIU interferon alfa-2b for 6 to 8 weeks as induction therapy followed by three 3-week maintenance treatments with 1/100- to 1/10-dose BCG plus 50 mIU interferon (titrated to symptoms) as maintenance therapy at months 5, 11, and 17. After a median follow-up of 30 months, 63% of patients were disease-free at 12 months and 53% were disease-free at 24 months. Adverse effects were generally no worse than with BCG alone.

Table 1. BCG Plus Interferon alfa-2b: Published Clinical Trials.

Study	No.	Tumor Type	Regimen	Dose	Outcome	Median F/U (Mo)
Stricker, 1996	7	CIS	IFN α-2b + 1/2-dose BCG*	10–100 mIU 60 mg	86% CR	12
	5	pTCC	IFN α-2b + 1/2-dose BCG*	10–100 mIU 60 mg	60% NED, 40% PR	12
Bercovich, 1995	18	pTCC	Full-dose BCG*	120 mg	RR = 28%	24
	18		IFN α-2b + 1/2-dose BCG	10 mIU 60 mg	RR = 22%	17
O'Donnell, 2001	40	Mixed, high risk	IFN α-2b + 1/3-dose BCG† + maintenance	50 mIU 27 mg	63% NED @ 12 mo 53% NED @ 24 mo	30

*Pasteur strain; †Connaught strain
NED = no evidence of disease; RR = recurrence rate

Stricker P. et al. *Urology*. 1996;48:957. Bercovich E, et al. *Arch Ital Urol Androl*. 1995;67:257. O'Donnell MA, et al. *J Urol*. 2001;166:1300.

As a result of these data, BCG/interferon combination therapy is increasingly being used in clinical practice and is being investigated by Dr. O'Donnell and others as first-line intravesical immunotherapy in the treatment of superficial bladder cancer. Dr. O'Donnell has reported preliminary findings indicating a disease-free rate of 68% at 2 years among high-risk BCG-naive patients treated with BCG/interferon. In the remainder of this *Tx Reporter*, Dr. O'Donnell answers some of the questions he has been asked by physicians regarding the implications of these data.

Q. What are the failure rates at 1, 2, and 5 years for initial treatment with BCG monotherapy, retreatment with BCG monotherapy following BCG failure, and retreatment with BCG/interferon following BCG failure?

Dr. O'Donnell: The following values are approximate (±10%), but I believe them to be reasonably accurate:

The failure rate with BCG as first-line therapy depends on patient and tumor characteristics. For the average group of patients with primary cancer, there is a 50% to 60% relapse rate at 5 years. The curve follows an exponential decay, with half of these recurrences occurring by 1 year, an additional 25% by the end of the second year, another 12.5% by the end of year 3, and then a relatively steady rate of recurrence of 3% to 5% per year thereafter. For selected subgroups of high-risk patients (eg, those with multifocal stage T1, grade 3 plus coexistent carcinoma in situ [CIS]), the ultimate rate of recurrence may be as high as 70% to 80%, with a median time to recurrence as short as 6 months and a similar type of exponential decay. For low-risk patients (eg, those with a primary stage Ta, grade 1–2, solitary lesion), the ultimate risk of recurrence may be only 30% to 40%, with a median time to recurrence of up to 2 years.

Data regarding failure rates with BCG retreatment are difficult to come by, since most studies have reported aggregate results of patients given one or two courses of BCG. Estimates also depend on risk groups, as described above, as well as on the time between first BCG treatment and recurrence. A late (>2 years) first recurrence tends to respond similarly to the original

primary cancer, whereas an early recurrence (by 3 months) tends to be more refractory to salvage BCG. A reasonable "average" estimate would be a failure rate of 60% to 70% by 5 years. Of these failures, about half occur within 6 months, about 70% within 12 months, about 90% by 2 years, and about 3%/y thereafter. It should be noted that the failure rate for a third cycle of BCG is about 80%, almost all within the first year and most within 6 months.

For BCG/interferon in patients who have previously failed BCG therapy, the failure rate is about 40% to 45% at 1 year, and 45% to 50% at 2 years. Over half of all failures occur by the first 3-month cystoscopy. The rate of failure after 2 years appears to be rather low (approximately 1% to 2%/y). Based on these findings, I would predict a failure rate of 50% to 55% at 5 years. My overall impression of the net benefit of BCG/interferon is an "absolute" 10% to 15% benefit in total durable complete response rate between 2 and 5 years versus BCG alone. Durable complete response rate is defined here as the proportion of patients with no evidence of disease (NED). In other words, the Kaplan-Meier curves are roughly parallel with an absolute differential of about 10% to 15%.

Q. What is the current standard of care for intravesical immunotherapy for superficial bladder cancer? Is it still BCG monotherapy, or is BCG/interferon now the standard?

Dr. O'Donnell: Standard of care is, by nature, a dynamic and evolving concept. Very encouraging evidence is now available supporting BCG/interferon combination therapy, including basic science data suggesting a synergistic effect, clinical data showing little increase in toxicity when these agents are combined, and emerging clinical data showing improved efficacy in patients at high risk for recurrence and those who have already failed first-line treatment with BCG. Moreover, BCG/interferon combination therapy was mentioned favorably by independent thought leader T. Keane in his commentary on a January 2001 review of intravesical therapy for superficial bladder cancer published in *Oncology*. In this commentary he wrote, "I do not feel a review of this topic is complete without a discussion of interferon alfa-2b (Intron A) and the impressive results being reported for its combination with BCG in high-risk primary and relapsing patients."

I believe that BCG/interferon combination therapy is intrinsically more active than BCG alone. However, without results from a phase III study (which is currently ongoing), I cannot advocate that BCG/interferon be used as first-line therapy for *all* patients with newly diagnosed transitional cell carcinoma (TCC) of the bladder. If the phase III study and cost-benefit analysis show that BCG/interferon is more effective than BCG alone and less costly in the long term—by reducing rates of transurethral resection of the bladder, for instance—then BCG/interferon may become the treatment of choice. In the meantime, however, it does have a role in appropriately selected candidates.

Q. Which patients are appropriate candidates for BCG/interferon combination therapy?

Dr. O'Donnell: At the current time, the most appropriate candidates for first-line BCG/interferon therapy are those with aggressive bladder cancer (eg, T1 grade 3 or multifocal CIS), who are likely to receive only a single course of intravesical therapy before being slated for a cystectomy. Combination therapy is also clearly indicated for patients with CIS or multifocal stage Ta grade 2–3 TCC who have already failed a course of BCG. Third, BCG/interferon is appropriate for any patient who has failed the "standard" 2 courses of BCG induction therapy but is not yet considered an appropriate candidate for cystectomy. For this last group of patients, chemotherapy regimens provide, at most, a 20% rate of durable response at 2 years, whereas my clinical data show a median 55% disease-free rate at 2.5 years with BCG/interferon.

Q. How should physicians choose BCG monotherapy, BCG/interferon combination therapy, or cystectomy for patients with stage T1 superficial bladder cancer?

Dr. O'Donnell: Generally, most patients (>80% in the United States and Western Europe) with stage T1, grade 3 disease receive at least one course of conservative therapy before consideration of cystectomy. They should first undergo a complete transurethral resection of bladder tumor (TURBT), with an immediate postoperative dose of intravesical chemotherapy to prevent tumor reimplantation, possibly followed by a "second-look" TURBT 3 weeks later to verify completeness of resection and to avoid the understaging that occurs in about 30% of cases. For immediate-postoperative chemotherapy, I prefer mitomycin C, 40 mg in 40 cc water for 30 minutes. TURBT should be followed 3 to 4 weeks later by intravesical immunotherapy. Monotherapy with BCG provides 5-year survival rates similar to those of cystectomy but allows about 60% of patients to retain their bladders. At the current time, we have no prospective data to prove that BCG/interferon combination therapy would be more effective than BCG alone, but several bits of evidence suggestively favor combination therapy—particularly the approximately 55% salvage rate for stage T1, grade 3 BCG failures, even among those who received two or three courses of BCG. For this reason I personally favor upfront BCG/interferon combination therapy for these high-risk patients, *even outside of a trial setting.*

Recommendations are less clear-cut for patients with stage T1, grade 3 disease who have already failed one course of BCG therapy, since these patients have a 50% or greater risk of progression to muscle invasion. The timing of recurrence influences prognosis, however. Herr reported that early recurrence of disease (by 3 months) is associated with an 82% rate of subsequent muscle invasion, uncontrolled local disease, or metastasis. Patients with recurrence of T1 cancer at 3 months also had a shorter median interval to progression (8.4 months) than those with a non–stage T1 lesion or no tumor found at 3 months (25% progression rate at a median of >5 years). Herr also estimated that a 3% to 5% chance of metastasis was incurred by waiting another 3 months from the time of

first failure. Thus, while all patients should at least be offered cystectomy at this point, a patient at high risk of surgical complications might be best treated with a second attempt at salvage therapy. Treatment must be individualized by considering (1) the tumor size and location, (2) the depth of lamina propria invasion, (3) the coexistence of CIS, and (4) whether there was some evidence of response to the initial course of therapy. Ultimately, the patient may steer the course of treatment by either pushing for or refusing cystectomy.

Q. Does a patient who is receiving treatment with BCG/interferon combination therapy require any additional monitoring or laboratory evaluation during treatment beyond what is standard for BCG monotherapy?

Dr. O'Donnell: No. In general, the side effects of BCG/interferon combination therapy are similar to those of BCG alone. In an evaluation of 1100 patients recruited into a multicenter phase II study of BCG/interferon, the only side effects more common with the BCG/interferon combination than with BCG alone included 10 cardiac events (ischemia, congestive heart failure, and arrhythmia), eight of which were thought not to be drug-related, and six reversible neurologic events (confusion, transient ischemic attack/cerebrovascular accident, weakness). Conversely, BCG/interferon is associated with fewer episodes of BCG sepsis than occur with BCG alone (0.1% with combination therapy versus 0.4% with BCG alone), due not only to the lower BCG doses used in the combination regimen but also to a protective effect of interferon alfa, which enhances BCG clearance.

Although not qualitatively different, side effects of combination therapy may sometimes be more severe for patients who originally experienced minimal side effects with BCG monotherapy. Patients who have received previous BCG treatment tend to experience side effects sooner and with greater intensity than BCG-naive patients. Side effects are also more common and more intense during maintenance treatments than with induction therapy, particularly during the second and third administrations in each maintenance cycle.

Q. By using BCG/interferon in clinical settings (ie, outside of clinical trials), are physicians putting themselves at legal risk, since this combination is not Food and Drug Administration (FDA) approved? Also, how can we persuade insurance companies to reimburse this treatment?

Dr. O'Donnell: Physicians have always had the ability and mandate to individualize therapy based on the available evidence and circumstances. It has been estimated by the American Society of Clinical Oncology (ASCO) that approximately half of all cancer patients receive anticancer drugs for off-label uses that are considered the standard of care for most cancers. ASCO has also pointed out that "the most effective chemotherapy regimens are typically combinations of two or more approved drugs, yet combination regimens are not usually reviewed or approved by the FDA. . . ." The National Cancer Institute reported in response to the 1989 Senate Appropriations Committee hearings that "the history of cancer drug development in our country shows that the most beneficial uses for new agents are generally discovered in the postmarketing phase, that is after a drug has been approved by the FDA for marketing of the labeled indication." In the field of urology, neither doxorubicin nor mitomycin C is FDA-approved for intravesical therapy of bladder cancer, although they are commonly used for this indication. Similarly, BCG was in use for over a decade before it was approved by the FDA for use in bladder cancer. Intravesical interferon alfa is listed as a second-line agent for treatment of superficial bladder cancer in the US Pharmacopeia (USP; see www.usp.org), and as such, meets the general guidelines for off-label drug use by Medicare and most third-party insurers. This information, as well as other available medical literature on combination therapy, can be shared with third-party payers and should protect physicians legally. TX

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