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# THE TREATMENT REPORTER UROLOGY

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## New Prospects in the Treatment of Superficial Bladder Cancer: A Case-based Approach

Dear Colleague:

If followed for a sufficiently long period, the vast majority of patients with superficial bladder cancer will experience disease recurrence or progression after primary treatment. Immunotherapy with intravesical Bacillus Calmette-Guérin (BCG) shows high efficacy, but dose-limiting toxicity may develop. While intravesical chemotherapeutic agents have demonstrated some decrease in recurrence rate, the effects are generally modest and tumor progression is unaltered. Furthermore, they are also associated with toxicities that at times can be significant. Thus, given the large number of patients with superficial bladder cancer who will experience recurrent or progressive disease and the toxicities associated with BCG and chemotherapy, new, less-toxic options are needed. Intravesical interferon alfa in combination with low-dose BCG is an effective alternative for patients at high risk for disease recurrence or progression whose disease is refractory to standard-dose BCG. In addition, combination therapy may be appropriate for patients who are potential candidates for cystectomy because of prior treatment failure.

We are pleased to offer you this educational activity, *New Prospects in the Treatment of Superficial Bladder Cancer: A Case-based Approach*, which provides an introduction to the use of interferon alfa in the treatment of superficial bladder cancer. An outstanding faculty of urologists describe patient cases and discuss treatment dilemmas and options. The cases and corresponding discussions provide practical strategies for approaching the management of superficial bladder cancer, especially among the more challenging clinical scenarios.

The goal of this newsletter, the first in a series of four, is to provide you with critical insight into the management of superficial bladder cancer in a patient with recurrent disease for whom radical therapy is medically inappropriate. This case-based activity, which is designated for 1 CME credit upon completion of the four-case series, is designed to update you on the latest findings from clinical trials and the implications for clinical practice.

We hope you find this series helpful and informative.

Sincerely,

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### Patient Description

The patient is a 79-year-old male who presents with significant urinary frequency, urgency, and moderate dysuria of about six months' duration. He had previously received a two-week course of a fluoroquinolone antibiotic from his primary care physician without clear improvement. He denies fever, chills, flank pain, or gross hematuria. He admits to a moderate decrease in his urinary force of stream, which has remained unchanged over the past year. His medical history is remarkable for two prior diagnoses of myocardial infarction, hypertension, chronic obstructive pulmonary disease, osteoarthritis, and a cerebral vascular accident with minimal motor deficit and mild memory loss. He was treated for tuberculosis 20 years ago. He has no current angina. Medications include atenolol, hydrochlorothiazide, and low-dose aspirin. He has a >50 pack-year history of smoking, but has not used tobacco for the last 15 years. He lives with his 78-year-old wife in an assisted-living facility and has good support from his extended family.

On physical exam, the patient is a thin, but essentially healthy-appearing, elderly man in no apparent distress. Examination of the heart, lungs, and abdomen is unremarkable. The prostate weighs approximately 45 grams and is nontender and without nodules.

(continued on page 2)



### Learning Objectives

This case-based educational activity is designed to update urologists on emerging treatment options for patients with superficial bladder cancer.

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

- Describe the clinical characteristics, staging, and grading of bladder cancer as they relate to clinical decision making
- Discuss the strengths and weaknesses of current treatments for both disease eradication and prevention of recurrence
- Describe the benefits of rIFN- $\alpha$ 2b as second-line monotherapy or in combination with BCG, as illustrated in selected case studies
- Apply the lessons learned from the case studies about the use of rIFN- $\alpha$ 2b to improve the clinical outcomes of patients with superficial bladder cancer

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

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Michael A. O'Donnell, MD, has indicated significant relationships with Eli Lilly and Co, MycImmune, and Schering-Plough.

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The urinalysis results reveal 1+ for blood on dipstick and show 1 to 3 red blood cells per high-power field (HPF), 0 to 2 white blood cells per HPF, and no bacteria. Prostate-specific antigen (PSA) level is 4.5 ng/mL, blood urea nitrogen (BUN) level is 24 mg/dL, and creatinine level is 1.5 mg/dL.

### Diagnostic Assessment

#### Question 1:

Which of the following diseases is LEAST likely to account for this patient's condition?

- Chronic nonbacterial prostatitis
- Bladder cancer
- Bladder calculus
- Renal cell carcinoma
- Neurogenic bladder

### Discussion

(d) With the exception of renal cell carcinoma, any of the conditions listed could account for irritative voiding symptoms. Of the possible diagnoses, bladder cancer should be considered foremost in this patient, because of his age and history of tobacco use. As many as 10% to 20% of patients with bladder cancer present with irritative voiding symptoms, and half of these patients present without significant hematuria. Carcinoma in situ (CIS) is the bladder cancer subtype most commonly associated with these findings.

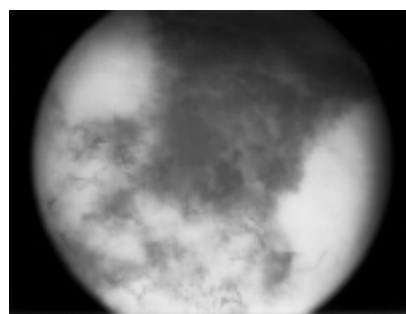


Figure 1. Carcinoma in situ: cystoscopic appearance.

### Case Continues

The patient's urine is evaluated, and the cytology result is strongly

suspicious for high-grade urothelial carcinoma. The result of an intravenous pyelogram is normal, except for moderate benign prostatic hyperplasia. Cystoscopy under anesthesia reveals patchy, raised, erythematous lesions without frank exophytic or papillary tumors (Figure 1). The histopathology report from the bladder biopsies reads "high-grade severe urothelial dysplasia."

### Initial Therapy

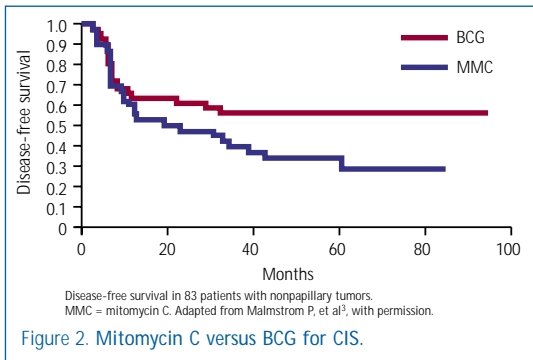
#### Question 2:

What is your initial choice of therapy for this patient?

- Observation only
- Repeat bladder biopsies and/or cytologies
- Mitomycin C intravesical chemotherapy
- Bacillus Calmette-Guérin (BCG)
- Radical cystectomy

### Discussion

(d) Bacillus Calmette-Guérin is the initial drug of choice. Repeat biopsies are unnecessary, since severe dysplasia and CIS are now considered the same entity, according to a recent Pathology Consensus Conference convened by the World Health Organization and the International Society of Urologic Pathology.<sup>1</sup> Considering that the progression rate for CIS is 50%, observation would not be advisable in this otherwise fully functional elderly man.<sup>2</sup> While mitomycin C may lead to an initial 40% to 50% complete response in patients with CIS, randomized controlled studies have found BCG to be superior, with durable complete responses approaching 60% (Figure 2).<sup>3</sup> Prior history of tuberculosis is not a contraindication to BCG therapy. Radical cystectomy would be premature, and would present an increased risk of complications for this particular patient.



**Case Continues**

A second six-week induction course of BCG is initiated. The patient develops significant local cystitis symptoms, intermittent hematuria, low-grade fevers, malaise, and joint aches, but is eventually able to complete therapy. He returns six weeks later for re-

**Case Continues**

Six weeks after completing a six-week induction course of intravesical BCG, the patient undergoes repeat cystoscopy. Multiple areas of diffuse redness are seen. Bladder wash is positive for high-grade transitional cell carcinoma (TCC). Bladder biopsies reveal multifocal CIS.

**Secondary Therapy**

**Question 3:**

What would you recommend for this patient with recurrent CIS?

- a. Mitomycin C
- b. Repeat BCG
- c. Valrubicin
- d. Radical cystectomy
- e. Systemic chemotherapy with or without radiotherapy

**Discussion**

(b) A second course of BCG has a 30% to 50% chance of rendering a patient with recurrent CIS disease free.<sup>4</sup> In contrast, a clinical study in which patients failing BCG therapy were crossed over to a mitomycin C regimen found that only 19% remained free of recurrence by three years.<sup>3</sup> In the setting of patients with at least two failures on BCG therapy, valrubicin has demonstrated an initial complete response rate of 21% at six months, but only 8% at two years.<sup>5</sup> Radical cystectomy is still premature in this elderly male with moderate comorbidities. Systemic chemotherapy, with or without radiotherapy, is generally ineffective against CIS.

evaluation. Results of a voided urine cytology are positive, and the bladder biopsies continue to show multifocal CIS. The patient adamantly refuses cystectomy.

**Salvage Therapy**

**Question 4:**

How would you handle this clinical situation?

- a. Observe for another three months before deciding
- b. Offer a third course of BCG or maintenance three-week miniseries of BCG every three to six months
- c. Start intravesical valrubicin
- d. Start intravesical interferon alfa
- e. Start combination low-dose BCG (one-third strength) plus interferon alfa

**Discussion**

(e) The patient's disease is refractory to BCG, and he is unable to tolerate further treatment with standard-dose BCG. While approximately 25% of patients with CIS will have a delayed complete response to BCG at six months after primary therapy, this is rarely seen after back-to-back treatment failure.<sup>6</sup> Even if the patient were able to tolerate another course of standard-dose BCG, a third course of BCG has a success rate of less than 20%.<sup>4</sup>

Maintenance BCG has not yet been evaluated in this setting. Valrubicin, while appropriate, is prone to causing cystitis and displays a durable response rate of only about 8% at two years (Table 1<sup>3-6,7</sup>).<sup>5</sup> Intravesical interferon alfa monotherapy is less irritating than other agents, but provides only a 12% durable response and is minimally active against BCG-refractory CIS.<sup>8</sup> Combination low-dose BCG plus interferon alfa provides a reasonable alternative to other conservative options, since it has shown a 55% complete response rate.<sup>7</sup> The protocol for this study included six treatments of BCG at one third the standard dose plus 50 million units (MU) of interferon alfa-2b. Three additional three-week miniseries, which included BCG with the dose titrated down by one-third increments as needed for tolerance, were given at 3, 9, and 15 months after the last induction dose. A reinduction arm with one tenth the standard BCG dose plus 100 MU interferon alfa was included for patients who showed an incomplete response to the first induction cycle.

**Case Continues**

Treatment is initiated with BCG at one third the standard dose plus 50 MU of interferon alfa. After the second treatment, the patient experiences moderate urinary symptoms, which resolve slowly over five days.

Table 1. Efficacy Comparison of Agents After BCG Failure

Author	Agent	Patient Group	N	2-year NED(%)
Catalona <sup>4</sup>	BCG, 3rd course	Mixed	6	20
Williams <sup>8</sup>	IFN $\alpha$	CIS-pure	34	12
Malmstrom <sup>3</sup>	MMC	Mixed*	19	23
Steinberg <sup>5</sup>	Valrubicin	CIS <sup>†</sup>	90	8
O'Donnell <sup>7</sup>	BCG + IFN $\alpha$	Mixed <sup>‡</sup>	21	55

\* For BCG failures x 1; crossover  
<sup>†</sup> All concurrent papillary TCC resected  
<sup>‡</sup> For BCG failures x 2+

NED = no evidence of disease; MMC = mitomycin C; IFN $\alpha$  = interferon alfa; mixed = patients with T<sub>a</sub>, T<sub>1</sub>, or CIS tumors; CIS-pure = patients with primary CIS tumors without papillary TCC.

## Improving Treatment Tolerance

### Question 5:

What step(s) should you take to increase the likelihood that the patient can tolerate this treatment regimen? (Select all that apply.)

- Provide urinary analgesics and antispasmodics as appropriate
- Delay dosing interval for two to three weeks
- Reduce BCG dose sequentially as needed, from 1/3 to 1/10, 1/30, or 1/100
- Reduce interferon alfa dose
- Add three days of oral isoniazid, beginning the day prior to planned treatment

### Discussion

(a), (b), and (c) may help the patient tolerate BCG plus interferon alfa combination therapy. A reduction in BCG dose, titrated to tolerance; a delay in dosing interval; and appropriate use of urinary analgesics and antispasmodics (even pretreatment narcotics) have allowed BCG-intolerant patients to continue with therapy and achieve high therapeutic success with the combination regimen.<sup>7</sup> (d) and (e) are unlikely to decrease local side effects and may actually compromise efficacy. While interferon alfa is tolerated at intravesical doses up to 1000 MU/week, it induces minimal cystitis.<sup>9</sup> Oral isoniazid therapy has been shown to

reduce neither local nor systemic toxicity from BCG.<sup>9</sup>

### Epilogue

This case study is based on an actual patient with multifocal CIS who had sequentially failed two courses of BCG. He had a dramatic response to low-dose BCG plus interferon alfa combination therapy, with complete resolution of cytologic and histologic evidence of CIS. Based on the SWOG 8507 study of miniseries maintenance,<sup>6</sup> two maintenance miniseries of very low-dose BCG and interferon alfa were given at three and six months. However, the patient eventually developed intolerance, necessitating discontinuation. He remained disease free for 2 1/2 years, but died following a hip fracture. At the time of his death, the patient had no evidence of recurrent TCC.

### Summary

While BCG remains the mainstay of treatment for CIS, many patients eventually fail BCG therapy, and the appropriate next course of action is a dilemma. Intravesical chemotherapy is generally a poor alternative to BCG, because of low durable response rates. Patients failing BCG therapy for the first time can be re-treated with BCG with a reasonable chance of

success. However, tolerance is often a problem, especially at the standard BCG dose. Indeed, recent clinical studies suggest that lower BCG doses may actually be more effective than higher doses for BCG-sensitized patients.<sup>10,11</sup>

After a second BCG failure, cystectomy is generally considered unless medically contraindicated. Interferon alfa monotherapy can be used as salvage therapy in a small percentage of these patients, but is most effective for patients who have relapsed beyond six months.<sup>8</sup> In early trials, BCG plus interferon alfa combination therapy appears promising when compared with BCG alone, for initial treatment and as an option for “salvaging” BCG-refractory patients.<sup>7,11,12</sup> A biologic basis for immune synergy has also been firmly established.<sup>13</sup> However, until confirmed in larger studies, BCG and interferon alfa combination therapy might best be reserved for high-risk patients for whom radical therapy is medically inappropriate. In addition, it may also be appropriate in place of standard BCG in cases where the next step after that BCG failure would otherwise be radical therapy<sup>TX</sup>

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# CME Posttest

## *New Prospects in the Treatment of Superficial Bladder Cancer: A Case-based Approach*

Release Date: April 30, 2001

### CME Instructions

During the next 24 weeks you will receive a total of 4 newsletters. To receive documentation of your participation in this 4-part CME activity for a total of 1 hour of CME credit, please complete the following steps:

1. Read each newsletter.
2. Complete the CME posttest included in each of the newsletters.
3. Mail or fax each of the completed posttests to Projects In Knowledge, One Harmon Plaza, Secaucus, NJ 07094; fax: 1-201-617-7333.\*
4. After reading the final newsletter, complete the CME evaluation survey contained therein.
5. Mail or fax your posttest and the CME evaluation survey to Projects In Knowledge (address above).

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Please indicate your answers below (circle one).

1. Irritative voiding symptoms may often be seen in patients with:
  - a. Renal cell carcinoma
  - b. Bladder cancer
  - c. Bladder calculus
  - d. Both b and c
2. Carcinoma in situ is:
  - a. Associated with a progression rate of 10%
  - b. Associated with a progression rate of 50%
  - c. Distinct from severe dysplasia
  - d. Both b and c
3. For patients with recurrent CIS after a single course of intravesical BCG:
  - a. A second course of BCG has a 30% to 50% chance of rendering the patient disease-free
  - b. A course of mitomycin C has only a 19% remission rate at three years
  - c. Without further therapy, there is an approximately 25% risk of delayed complete response to BCG by six months
  - d. All of the above
4. Combination therapy with low-dose BCG plus interferon alfa:
  - a. May be better tolerated with a reduced BCG dose
  - b. Is rarely associated with cystitis
  - c. May be better tolerated with oral isoniazid prior to planned treatment
  - d. Has shown a 5% complete response rate