Dear Colleague:

Treating patients with recurrent low-grade, low-stage transitional cell carcinoma (TCC) of the bladder presents a significant challenge for urologists. Controversies regarding the use of adjuvant intravesical therapy for these patients arise because of the potential toxicities of therapeutic agents despite their documented efficacy. Thus, management of recurrent low-grade TCC requires a thorough understanding of the available treatment options to optimize prevention of disease progression and recurrence while minimizing risk of toxicities. Intravesical interferon alfa is a viable treatment option for patients who cannot tolerate frequently occurring side effects seen with other intravesical agents.

We are pleased to offer you New Prospects in the Treatment of Superficial Bladder Cancer, a CME newsletter addressing the use of interferon alfa in the treatment of recurrent low-grade superficial bladder cancer. This case-based CME activity presents the case of a surgeon with recurrent low-grade, low-stage TCC who requires adjuvant therapy to enable him to sustain his professional work in the operating room. It provides practical strategies for approaching this management dilemma and updates you on the latest findings from clinical trials and their implications for clinical practice.

This newsletter is the third in a series of four. Physicians can receive 1 hour of CME credit upon completion of the four parts. It is designed to provide you with critical information that will translate into practical clinical application. Don’t miss this opportunity to gain the knowledge you can in turn offer your patients so that they may improve their quality of life.

We hope you find this series helpful and informative.

Sincerely,

Michael A. O’Donnell, MD
CME Activity Chair
Associate Professor and Director of Urologic Oncology
Department of Urology
University of Iowa
Iowa City, IA

Steven I. Cohen, MD
Assistant Clinical Professor of Urology
Brown University School of Medicine
Providence, RI
Boston University School of Medicine
Boston, MA

Patient Description

The patient is a 62-year-old male surgeon, and a colleague of mine who stopped me in the hospital locker room to report an episode of painless gross hematuria. After completing his surgical case, he voided a full stream of painless gross hematuria. By the next void, his urine had cleared. He also admitted to urgency. He has no prior history of stone disease or urologic abnormalities.

His past medical history is significant for cigarette smoking (>40 pack-years), and he still smokes occasionally. He was purified protein derivative (PPD) positive in medical school and was treated for one year with isoniazid. His surgical history is positive for a prior cholecystectomy and for a splenectomy after trauma.

His physical exam reveals a normal healthy-appearing male. Examination of his head, neck, and chest is negative. His abdomen is benign to palpation. Two old surgical scars are seen. His bladder is nonpalpable. Testes are descended, without any evidence of intrascrotal masses or tenderness. The prostate is benign, without any evidence of fluctuance; it is nontender, and no 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-α2b 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-α2b to improve the clinical outcomes of patients with bladder cancer

CME Information

Projects In Knowledge is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor CME for physicians. 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.

This independent CME activity is planned and produced in accordance with the ACCME Essentials and Standards for Commercial Support.

Disclosure Information

The Disclosure Policy of Projects In Knowledge requires that 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.

This independent CME activity is supported by an unrestricted educational grant from Schering-Plough.

Case Continues

The laboratory urinalysis (UA) reveals 6–10 red blood cells per high power field (HPF), 1–2 white blood cells per HPF, and negative urine cultures. Cytology is ‘atypical’. An intravenous pyelogram reveals normal upper tracts with a small postvoiding residual, and a possible 2-cm filling defect on the posterior wall of the bladder.

Cystoscopy under anesthesia reveals a single 2.5-cm papillary bladder tumor on the right posterior wall. A transurethral resection of the bladder tumor (TURBT) reveals a Ta grade 2 transitional cell carcinoma (TCC). Postoperative course is uneventful.

Initial Assessment

Question 1:
Which one of the following diseases is most likely in this patient?

a. Bladder stone with obstruction
b. Bladder cancer
c. Ureteral calculus
d. Chronic retention with urinary tract infection (UTI)
e. Bacterial prostatitis

Discussion

(b) Bladder cancer is frequently associated with painless, gross or microscopic hematuria. In fact, this presentation is seen in approximately 85% of patients. The fact that this patient has a long history of smoking increases his risk of bladder cancer. Given the lack of previous urologic voiding problems, UTIs and retention are much less likely. The absence of flank pain and colic make ureteral calculus less of a probability. Bacterial prostatitis is generally associated with lower urinary tract symptoms.

Case Continues

The laboratory urinalysis (UA) reveals 6–10 red blood cells per high power field (HPF), 1–2 white blood cells per HPF, and negative urine cultures. Cytology is ‘atypical’. An intravenous pyelogram reveals normal upper tracts with a small postvoiding residual, and a possible 2-cm filling defect on the posterior wall of the bladder.

Cystoscopy under anesthesia reveals a single 2.5-cm papillary bladder tumor on the right posterior wall. A transurethral resection of the bladder tumor (TURBT) reveals a Ta grade 2 transitional cell carcinoma (TCC). Postoperative course is uneventful.

Initial Management

Question 2:
Which indication does NOT require immediate intravesical adjuvant therapy?

a. Noninvasive Ta grade 3 TCC
b. Multiple (more than 2) Ta grade 2 lesions
c. Single, superficial, Ta low-grade tumor
d. History of recurrent, multiple, grade-1 lesions within the past 3 years

Discussion

(c) The indication for intravesical therapy is based on the risk of progression and recurrence, which is correlated with tumor multiplicity, size, stage, and grade. Low-grade disease may be well controlled by TUR only. Therefore, “C” is the correct answer.

Case Continues

No intravesical therapy is given. At six-month follow-up, the cystoscopy is negative. At one-year follow-up, the cystoscopy reveals three small papillary tumors posteriorly at the junction of the old scar, and two other lesions measuring 1.5 cm on the left lateral wall. Postresection pathology reveals all to be Ta grade 2 tumors.
Recognizing that his disease is now multifocal, we discuss the need for adjuvant intravesical therapy. I recommend Bacillus Calmette-Guérin (BCG). My colleague researches BCG on the Internet. Understanding the toxicity of BCG, he realizes that severe cystitis would interfere with his work, since severe urgency or frequency would not allow him to complete a cholecystectomy.

**Secondary Management**

**Question 3:**
What would you recommend for the treatment of this patient with recurrent tumor?

a. Full-dose BCG  

b. Reduced-dose BCG (1/10 dose only)  

c. Mitomycin C  

d. Radical cystectomy  

e. No therapy, observation only

**Discussion**

(c) With recurrence and multifocality, his risk of progressive disease is increased. Therefore, observation only is not warranted.

Because the patient has superficial, completely resectable disease, radical cystectomy would be premature at this time. Reduced-dose BCG requires an additive immunomodulator, interferon alfa, to maintain its efficacy. As shown in Table 2, full-dose BCG is more effective than mitomycin C. However, full-dose BCG is associated with greater toxicities, and is not recommended for this particular patient. Therefore, the correct answer is “C.”

**Case Continues**

Concerned about recurrences within one year and multifocality, he agrees to adjuvant therapy. Due to the BCG toxicity profile, he elects mitomycin C therapy. After induction with mitomycin C, interval cystoscopy reveals one small 0.5-cm papillary tumor, Ta grade 2. Immediately after completion of the TUR, 40 mg mitomycin C and 50 cc sterile saline are placed into the bladder at the time of TURBT, thereby reducing the risk of reimplantation recurrence.

By his second maintenance dose of mitomycin C, my friend is voiding with intermittent hematuria between each of his operating-room cases. Follow-up cystoscopy is negative but, given his symptoms, he wants to consider the option of a sole agent with demonstrated TCC activity but minimal, easily treatable side effects.

**Maintenance Therapy**

**Question 4:**
Which agent would you recommend for this patient for maintenance therapy?

a. Full-dose BCG  

b. Reduced-dose BCG (1/10 dose only) monotherapy  

c. Mitomycin C  

d. Interferon alfa  

e. Doxorubicin

**Discussion**

(d) Interferon alfa has demonstrated TCC activity, and yet may have minimal, easily treatable side effects. As outlined in Table 3, there is generally no dose-limiting effect.
toxicity up to 1,000 million units (MU) per dose. Full-dose BCG is an option, but the risk of adverse reactions (listed in Table 1) excludes this as an acceptable option for a patient who wants to continue his work as a surgeon. Reduced-dose BCG monotherapy has no data to support its efficacy. Mitomycin C and doxorubicin share a similar effectiveness and toxicity profile. Since hematuria has already developed with mitomycin C, doxorubicin would not be a beneficial choice for this patient. Therefore, high-dose interferon alfa (100 MU per dose) is a reasonable option, because of the low risk of adverse events and easily treatable side effects.

**Case Continues**

The patient is maintained on intravesical interferon alfa at 100 MU in 40 cc sterile saline as maintenance therapy. He is currently tumor-free, can finish a colectomy without symptoms, and the urinals remain clean.

**Summary**

Low-grade, low-stage disease is the most common form of bladder cancer the clinician will see. Certainly, with small-volume disease that is noninvasive and nonprogressive, TURBT management alone is effective and reasonable. Concern for implanting cancer cells on injured mucosa has always been considered, and recent work suggests that single-dose chemotherapy at the time of TURBT reduces the risk of rapid recurrence. BCG is known to be approximately 50% effective overall in delaying recurrence and progression. The price one pays is a very significant and severe morbidity profile. For my patient, this profile was unacceptable, and a less toxic agent with a minimal side-effect profile was needed. Interferon alfa is associated with cystitis toxicity in approximately 10% of patients, but these symptoms are easily controlled with local effective agents and nonsteroidal anti-inflammatory drugs (NSAIDs). Due to the morbidity profile of BCG and chemotherapy, patients with low-grade, low-stage disease may find interferon alfa, with its more benign toxicity profile, a viable option with minimal risk.

**Table 3. Toxicity of Intravesical Interferon alfa**

- Most common: “flulike” symptoms, fever
- Incidence 0%–19% in large studies
- No dose-limiting toxicity up to 1,000 MU/dose
- Side effects easily controlled with NSAIDs


**References**


CME Posttest

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

Original Release Date: April 30, 2001

CME Instructions

Over a period of 24 weeks you will receive a total of four newsletters. To receive documentation of your participation in this four-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. All four posttests and the evaluation must be received by October 30, 2002, for you to be eligible to receive CME credit.
5. Mail or fax your posttest and the CME evaluation survey to Projects In Knowledge (address above).

*At the end of the series, Projects In Knowledge will mail you an acknowledgment of your participation in this activity if your combined score for all four posttests is 70% or better. If your combined score is lower than 70%, you will be notified by mail and will be given an opportunity to retake the test.

Name ________________________________________________________________________ Degree ____________________
Mailing Address ___________________________________________________________________________________________
City ___________________________________________________________________ State _______ ZIP________________
Phone #______________________________________________ Fax # ______________________________________________
E-mail ___________________________________________________________________________________________________

Please indicate your answers below (circle one).

1. Bladder cancer typically presents with:
   a. Slow stream
   b. Flank pain
   c. Hematuria
   d. Fever

2. CIS or Grade 3 non-invasive TCC is appropriately treated by:
   a. Immediate cystectomy
   b. Systemic chemotherapy
   c. Radiation therapy
   d. Intravesical therapy

3. Side effects of intravesical interferon alfa include:
   a. Sepsis
   b. Flulike symptoms
   c. Hemorrhagic cystitis
   d. Contracted vesical volume

4. Patients who are immunocompromised or completely intolerant of intravesical BCG have no intravesical therapeutic option and should proceed to immediate cystectomy for CIS and/or Ta Grade 3 TCC:
   a. True
   b. False