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

Dear Colleague:

Immunotherapy with intravesical Bacillus Calmette-Guérin (BCG) is considered the gold standard for initial treatment of superficial bladder cancer. However, approximately 30% of patients treated with the agent will develop persistent or recurrent disease. Management of patients with persistent or recurrent disease should include consideration of various therapeutic options. Intravesical interferon alfa is one such option. As monotherapy, interferon alfa has shown salvage rates as high as 66% in patients with BCG-refractory carcinoma-in-situ. In addition, recent data suggest that the combination of BCG and interferon are associated with response rates of up to 65% at one year.

We are pleased to offer you this educational program, New Prospects in the Treatment of Superficial Bladder Cancer, which provides a case-based 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 second in a series of four, is to provide you with critical insight into the management of superficial bladder cancer in a patient with persistent low-grade transitional cell carcinoma of the bladder. This case-based program, 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 54-year-old male who presents with a 1-month history of intermittent, painless, gross hematuria. The patient has no significant past medical history except an inguinal hernia repair at age 45. He stopped smoking 10 years ago and is an auto mechanic. He describes mild nocturia, voiding once or twice nightly. Physical examination is unremarkable.

Evaluation includes an excretory urogram, urine culture, urinary cytology, and cystoscopy. The urogram reveals a bifid renal pelvis on the left, with the suggestion of a filling defect on the left bladder base. Urine culture is negative. Cytology is suspicious for low-grade transitional cell carcinoma (TCC). A 2-cm lesion is found at the left bladder base behind the trigone, with several smaller papillary lesions near the left bladder neck. The patient undergoes a transurethral resection of the bladder tumor (TURBT) with random bladder biopsies. Pathology is consistent with multifocal Ta grade 1–2 TCC. There is no carcinoma-in-situ (CIS), but mild dysplasia is observed in two of the random biopsies. The TUR specimen of the large tumor includes the muscularis propria. p53 staining of the specimen is negative.

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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 superficial bladder cancer

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

Projects In Knowledge Designates this 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 Oncology/Biotech.

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.

Leonard G. Gomella, MD, has indicated a significant relationship with Schering Oncology/Biotech.

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

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Initial Assessment

**Question 1:**
This patient is considered a candidate for initial intravesical therapy based on which adverse feature of his bladder tumor?

a. Mild dysplasia is present in two of the random biopsies
b. Ta disease is present
c. Multifocal TCC is found on initial presentation
d. p53 staining of the specimen is negative
e. This is a low-grade bladder cancer, and thus intravesical therapy is not indicated

Discussion

(c) Intravesical therapy can eradicate existing tumors, prevent progression and recurrence, and is recommended for patients at high risk for recurrence or progression. However, not all patients with superficial TCC require intravesical therapy (Table 1). Multifocality indicates a higher degree of urothelial instability, which translates into higher recurrence rates. The 1-year recurrence rates of 22%, 48%, and 75% for patients with one, two, and three or more tumors, respectively, have been reported. Mild dysplasia and Ta disease are not considered adverse features of TCC. Multifocal TCC is found on initial presentation, while p53 staining of the specimen is negative. This is a low-grade bladder cancer, and thus intravesical therapy is not indicated.

Secondary Management

**Question 2:**
In patients with persistent low-grade TCC following an initial course of BCG, the most reasonable strategy is:

a. Immediate cystectomy
b. Bilateral retrograde pyelograms with brush biopsies of both renal pelves
c. Intravesical chemotherapy
d. A repeat 6-week course of BCG
e. Monthly maintenance BCG for 1 year

Discussion

(d) A single 6-week course of BCG may be inadequate, but some nonresponders may require an additional course of BCG before moving to salvage therapies. Seventy percent of patients treated with a second 6-week course remain tumor free for up to a year compared with 35% of patients treated with a single
6-week course of BCG, suggesting that another course of BCG is appropriate. A SWOG study that compared a single 6-week course of BCG with a 6-week course followed by an additional 3-week course at 3 months found a significant 25% complete response rate in the group treated with the additional 3 weeks of BCG. Radical cystectomy is not indicated at this point since there is no evidence of progression in stage or grade and no evidence of disease invasive to the muscle. Upper-tract studies are not needed since the result of the initial upper-tract imaging was negative, and recent urinary cytology finding is negative. Intravesical chemotherapy has not proven to be consistently effective after a failed course of BCG and maintenance will not convert a nonresponder into a responder.

Case Continues

A second 6-week course of BCG is given. A posttreatment biopsy of the bladder shows several new small tumors surrounding the left ureteral orifice. A retrograde pyelogram is unremarkable except for the bifid renal pelvis. The patient has no specific urologic complaints. The pathologic specimen shows multifocal, low-grade Ta, grade 1–2 TCC. The patient is concerned about the possibility of invasive bladder cancer, and a computed tomography scan of the abdomen and pelvis is ordered. Results of the procedure are completely normal, with no evidence of bladder wall thickening. The patient declines an offer for referral to a local cancer center for investigational protocols.

### Management of Refractory Superficial Bladder Cancer

#### Question 3:
Which statement is true about a patient with low-grade, low-stage superficial bladder cancer who has failed two 6-week cycles of BCG?

- a. Intravesical chemotherapy with mitomycin C is the standard of care and can achieve salvage rates of over 50%
- b. Interferon alfa-2b, either alone or in combination with BCG, has been reported to have response rates between 25% and 50% in patients with BCG-refractory disease
- c. A third course of BCG should be attempted, using an alternate strain
- d. Intravesical valrubicin is indicated in all patients with BCG-refractory disease
- e. Immediate cystectomy is indicated

#### Discussion
(b) As intravesical monotherapy, interferon alfa-2b has shown activity with a low-toxicity profile. Salvage rates as high as 66% have been reported for patients relapsing with CIS following BCG treatment, with lower rates (25%-40%) for patients with papillary disease. Recent data suggest that the combination of BCG and interferon alfa is synergistic, with response rates of up to 65% at 1 year. While not FDA approved for this use, the US Pharmacopoeia lists interferon alfa as second-line therapy in superficial bladder cancer.

Although BCG is arguably the “gold standard” for superficial bladder cancer, recurrences are reported in up to 30% of patients. Herr et al reported a progression rate of 38% and disease-specific mortality rate of 25% in BCG-treated patients who were followed for 10 years. The BCG strains used today were originally derived from the Pasteur strain developed by Albert Calmette and Camille Guérin in the late 19th century. Several other strains have been developed with differing biological activity, which could result in different levels of efficacy. All FDA-approved BCG strains have been shown to be effective in the management of superficial TCC, but there are no data to support administration of a third course of BCG using an alternate strain.

Valrubicin, an adriamycin analogue, is the only FDA-approved regimen for BCG-refractory bladder cancer, with a reported response rate of 21%. Valrubicin is indicated for intravesical therapy of BCG-refractory CIS of the urinary bladder in patients for whom immediate cystectomy would be associated with unacceptable morbidity or mortality. Standard intravesical chemotherapy (mitomycin C) has not been shown to be a reliably effective salvage therapy in patients failing BCG.

Radical cystectomy is indicated for refractory, diffuse, high-grade T1 lesions, CIS, or tumors with prostatic stromal involvement. It is also recommended for patients with T1 grade 3 TCC refractory to BCG. This patient has low-risk bladder cancer; additional salvage therapies should be attempted. If the patient demonstrates progression to a higher grade or stage (ie, T1 G3), immediate cystectomy or a bladder preservation protocol should be offered.

Case Continues

The patient receives 6 weeks of intravesical mitomycin C at a dose of 40 mg. Follow-up cystoscopy and biopsy demonstrate two new papillary lesions on the left lateral wall. Results of random biopsies are negative. Pathologic examination...
again demonstrates a Ta grade 2 TCC. Having failed two cycles of BCG and mitomycin-C, the patient is treated with intravesical interferon alfa-2b for 6 weeks at a dose of 100 million units in 50 cc sterile water. The patient reports mild malaise after each instillation, but no lower-tract symptoms. Cystoscopy and bladder biopsy specimens demonstrate no visible lesions, and histologic examination of biopsy specimens shows areas of denuded mucosa, but no cancer.

### Follow-up of Superficial TCC

**Question 4:**

What is the recommended follow-up protocol for patients with successfully treated superficial TCC of the bladder?

- **a.** Cystoscopic follow-up is not needed for low-risk bladder cancer
- **b.** Urinary cytology, with cystoscopy and biopsy only if the cytology is positive
- **c.** Cystoscopy and cytology every 3 months for 2 years, then every 6 months
- **d.** Urinary tests, such as NMP-22 or BTA STAT, every 3 months for 2 years, then every 6 months
- **e.** Monthly cystoscopy and cytology for life

### Discussion

(c) The follow-up protocol recommended for patients with superficial TCC includes cystoscopy and urine cytology every 3 months for 2 years, then every 6 months for 2 years, and then yearly thereafter. Annual excretory urography is also recommended, although this recommendation is not uniformly accepted.

Whether or not to continue long-term cystoscopic surveillance for low-grade papillary tumors is disputed. The annual incidence of first recurrence declines rapidly in the first 2 years but remains steady for up to 8 years. While some experts recommend continued cystoscopic surveillance, others suggest stopping cystoscopy after 5 years if there has been no recurrence. As demonstrated by this patient, most superficial low-grade papillary tumors will have recurrences of the same grade and stage.

Urinary cytology has a low sensitivity in diagnosing low-grade tumors. The use of newer urinary tests, such as BTA-Stat and NMP-23, may improve detection rates or alter our standard follow-up, but these tests need further validation.

Data from Sloan-Kettering that showed patients with high-risk tumors may progress at a later time. Investigators found a high incidence (21%) of upper-tract tumors in patients with high-grade bladder lesions. These upper-tract tumors developed after an average of 7.3 years. Patients with high-grade superficial TCC should have continued upper-tract surveillance. The value of upper-tract surveillance for patients with lower-grade cancer is disputed.

### Conclusions

The management of superficial bladder cancer continues to progress, leading to improved outcomes for patients with the disease. TUR with intravesical BCG is considered the gold standard, but approximately 30% of patients undergoing this regimen will have persistent or recurrent disease. Salvage therapies for patients with BCG-recurrent disease continue to improve, with a growing interest in combination immunotherapies and intravesical gene therapies. The ongoing efforts to find a uniformly reliable predictor of therapeutic response and alternative therapies to lower toxicity but not efficacy will continue to improve the management of superficial bladder cancer.

### References

Erratum

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

A statement printed in the letter from the faculty in the June 14, 2001, release of the Urology Treatment Reporter which states, “As monotherapy, interferon alfa has shown salvage rates as high as 66% in patients with BCG-refractory carcinoma-in-situ,” may have been misleading. The statement should have read: “As monotherapy, interferon alfa is a valuable option to consider in patients with carcinoma-in-situ who have failed prior BCG, because of interferon alfa’s low-toxicity profile.”

In an article on the role of interferon alfa in superficial bladder cancer, Belldegrun et al reviewed studies conducted in patients with CIS who had previously failed BCG. Although one study showed a response rate of 66%, it is important to note that the study cohort consisted of only 9 patients. In addition, out of the 6 responders, only 2 responded completely (22%). In a follow-up study of 34 patients, the initial 3-month complete-response rate was 40%. However, by the end of 6 months, all the truly BCG-refractory patients (n = 10) failed, while only 4 of 20 patients (20%) who had previously responded to BCG but failed later, maintained a long-term durable complete clinical response. The review article showed an aggregate durable complete clinical response rate of 18% to interferon monotherapy among the studies discussed. Therefore, intravesical interferon, alone or in combination with BCG, is an option clinicians may consider as salvage therapy in patients with superficial bladder cancer who have failed prior BCG.

Reference
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 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. 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.

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Please indicate your answers below (circle one).

1. Intravesical therapy:
   a. Is indicated for all patients with superficial TCC
   b. Can eradicate existing tumors
   c. Can prevent progression
   d. Both b and c

2. Which is true about the use of BCG for low-grade TCC?
   a. A single 6-week course is generally adequate therapy
   b. A second course of BCG does not improve tumor-free rates
   c. Once a patient has failed BCG, radical cystectomy should be performed
   d. Persistent low-grade TCC can be treated with additional courses of BCG

3. Which is FALSE about interferon alfa-2b?
   a. The combination of BCG and interferon alfa-2b appears to be synergistic
   b. The response rate for combination therapy with BCG and interferon alfa is approximately 13% at 1 year
   c. Salvage rates with interferon alfa-2b monotherapy are as high as 66% for patients with CIS failing prior BCG treatment
   d. The US Pharmacopeia lists interferon alfa as second-line therapy in superficial bladder cancer

4. Which is true about recommended follow-up for patients with successfully treated superficial TCC?
   a. Excretory urography is clearly indicated every year
   b. Urine cytology has a high sensitivity in diagnosing low-grade tumors
   c. The recommended timing for follow-up cytoscopy and cytology is every 3 months for 2 years, every 6 months for 2 years, then yearly thereafter
   d. Urinary tests, including NMP-23, are recommended annually for follow-up