Patient Description

A 53-year-old man presents with gross, total, painless hematuria and is found on cystoscopy to have a solitary 2-cm tumor adjacent to the right ureteral orifice. The tumor has a broad base and is irregular in appearance. His health is otherwise good, and he stopped smoking 10 years ago.

Diagnostic Assessment

Question 1:
What diagnostic step(s) is (are) important in this case?

a. Careful resection to include all tumor(s) and biopsy to include muscle
b. Upper tract imaging study
c. Bimanual examination to exclude palpable residual or extravesical tumor
d. Random bladder and prostatic urethra biopsy
e. All of the above

Discussion

(e) The initial diagnostic approach for this case would be to completely resect the tumor, carefully inspect the entire bladder, and do a bimanual examination under anesthesia to be certain that no other tumors are present and that the tumor is completely resected. Occult invasive disease is common in patients with this type of presentation. In a review of 101 patients who underwent cystectomy for clinical stage T1 grade 3 disease, 30% were found to have unsuspected muscle invasion or metastatic disease.2 The evaluation of
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

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Donald L. Lamm, MD, has indicated significant relationships with Schering Corporation, Aventis Pharmaceuticals, and Organon Inc.

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

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Initial Management

Question 2:
After complete tumor resection, what is the optimal management of a person who presents with a solitary, 2-cm, T1 grade 3 tumor?

a. Observation
b. Repeat transurethral resection in 1 to 2 weeks
c. Immediate single-dose chemotherapy
d. Intravesical BCG immunotherapy 2 weeks after resection
e. Radical cystectomy with orthotopic neobladder reconstruction

Discussion

The EORTC has correctly concluded from their many controlled trials that BCG is superior to chemotherapy in reducing tumor recurrence and that none of the available chemotherapies is superior to any of the other current chemotherapeutic agents. While immediate instillation of chemotherapy clearly improves the results of intravesical chemotherapy, immediate BCG instillation should never be used. There is no evidence of improved response with early BCG instillation, and the risk of systemic absorption and sepsis is greatly increased. BCG treatment should be delayed for 2 weeks after tumor resection.

The management of T1 grade 3 bladder cancer remains controversial. However, controlled studies have confirmed that intravesical BCG immunotherapy is superior to chemotherapy. Prior to the advent of BCG immunotherapy, approximately 43% of patients with T1 grade 3 disease progressed to muscle invasion or metastasis within 5 years (see Table 1). Thus, observation would not be an appropriate option for management of this patient’s disease. The presence of CIS, p53 abnormality,
vascular invasion, or multifocality increases the already high risk of disease progression.

Current series of T1 grade 3 patients treated with what we now know to be suboptimal BCG regimens (3-week maintenance) show 5-year progression rates of less than 15% (see Table 1).7 Remarkably, these 5-year progression rates are significantly less than the 30% to 40% rates in patients who have stage T2 or higher disease and underwent cystectomy for suspected T1 disease. In addition, the 5-year survival rate in patients undergoing cystectomy for muscle invasive disease is only 45%.8 A series of selected patients suggest that one might avoid the morbidity and 2.5% mortality of major surgery and still provide a survival advantage by giving BCG.

Remarkably, computer modeling projects an 86% 5-year survival rate for patients who undergo immediate cystectomy for T1 grade 3 disease that was confirmed by histology to be PO at the time of surgery, while those who are first treated with BCG immunotherapy and have cystectomy done at the time of treatment failure have a 5-year survival rate of 91%.9

Many European urologists recommend repeat resection in 1 or 2 weeks when T1 grade 3 tumors are found, based on the frequent (40%) finding of residual disease and the concern that occult muscle invasive disease may be present. In my opinion, the residual disease seen in these patients is more often the result of seeding at the time of surgery rather than of incomplete resection. I would therefore initiate treatment and delay biopsy to confirm complete absence of disease until the 3- or 6-month follow-up cystoscopy.

Cystectomy is highly effective treatment, and orthotopic bladder substitution and nerve-sparing techniques make the procedure more palatable. My recommendation, however, would be to begin with BCG immunotherapy and reserve cystectomy for those who do not have a complete response.

Case Continues
At 3 months, the patient has a recurrent tumor at the dome, which is resected and found to be stage Ta grade 2.

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Rate (%)</th>
<th>Follow-up (Months)</th>
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<td>27</td>
<td>48</td>
<td>36</td>
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<tr>
<td>RUTT 1985</td>
<td>430</td>
<td>31</td>
<td>60</td>
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<tr>
<td>Malmstrom 1987</td>
<td>7</td>
<td>43</td>
<td>60</td>
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<tr>
<td>Jakse 1987</td>
<td>31</td>
<td>33</td>
<td>60</td>
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<tr>
<td>Kaubisch 1991</td>
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<tr>
<td>Mulders 1994</td>
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<td>27</td>
<td>48</td>
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<tr>
<td>Klan 1995</td>
<td>17</td>
<td>65</td>
<td>72</td>
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<tr>
<td>Holmang 1997</td>
<td>58</td>
<td>48</td>
<td>84</td>
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<tr>
<td>Total</td>
<td>636</td>
<td>43%</td>
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Table 1. Natural (TUR only) and Chemotherapy-Treated, History of T1 Grade 3 TCC

<table>
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<th>Author</th>
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<th>Rate (%)</th>
<th>Follow-up (Months)</th>
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<td>Klan 1998</td>
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<td>43</td>
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<tr>
<td>Total</td>
<td>698</td>
<td>13.8</td>
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</table>

*Includes 6 patients with grade 2 TCC.

Data from Esuvaranathan E, et al.7

Secondary Management

Question 3:
What further treatment would you recommend?

a. Observation
b. Three additional weekly BCG instillations, then 3-week maintenance
c. Six additional weekly instillations of BCG plus interferon alfa-2b 50 MU
d. Immediate chemotherapy
e. Immediate radical cystectomy

Discussion

The results of treatment with maintenance BCG alone are excellent,10 and those who fail with recurrent Ta or T1 disease whose treatment is unsuccessful can undergo rescue therapy with the combined BCG/alfa interferon treatment. A controlled comparison conducted by Esuvaranathan et al of full-strength Connaught BCG, one-third strength BCG, and one-third strength BCG plus interferon alfa-2b found combination therapy to significantly reduce tumor recurrence.7 Therefore, one could recommend combination BCG plus interferon as the initial treatment in high-risk patients with T1 grade 3 disease. Those with recurrence despite BCG would be even better candidates for the combined treatment.

Considerations in the treatment recommendation would include the patient’s financial status, since the combination treatment is significantly more expensive; his or her philosophy, ie, whether he or she would prefer to have “two throws of the dice” and a “safety net” rather than one throw with a better chance of initial success; and the risk factors. Patient risk factors that favor initial combination treatment include multiple tumors, tumors more than 3 cm in diameter, associated CIS, vascular invasion, invasion...
beyond 1.5 mm or the muscularis mucosa, and physical condition that would preclude cystectomy.

The addition of three weekly BCG instillations at 3 months increases the complete response rate in CIS from 69% to 84%, and up to three instillations every 6 months in patients who are disease free significantly reduces disease recurrence and progression. It is important to note that maintenance BCG should never be pushed to toxic levels. Patients should not receive BCG treatment until all of the side effects from previous treatments have resolved, and the second or third of the three weekly instillations should be discontinued if increased side effects occur with the first or second instillation. Patients who develop increasing side effects are at risk of major systemic toxicity, and increased side effects should be prevented by reducing the dose of BCG to 1/3, 1/10, or 1/100 dose in patients with escalating local side effects. The marked beneficial response to 3-week maintenance BCG in our Southwest Oncology Group study occurred despite omission (as recommended by protocol toxicity-reduction guidelines) of a scheduled 6-month maintenance treatment in 84% of patients.

I would avoid a second 6-week course of BCG, because patients who have had an initial course of BCG often show a suppressed immune response after the fourth, fifth, and sixth instillations during the second course.

## Controlled comparison of maintenance using repeated 6-week instillations every 6 months for 2 years showed no advantage over induction alone. In contrast, for reasons that have not yet been elucidated, the addition of interferon to BCG prevents immunosuppression, so a second 6-week course of BCG with interferon could be used.

## Case Continues

After having moved away from the area, the patient returns 4 years later. He received no further treatment after his “6 plus 3” induction of BCG and had remained free of tumor recurrence. Cystoscopy shows two recurrent tumors at the anterior bladder neck, and resection shows stage Ta grade 3 disease, with a focus of CIS on random bladder biopsy. The upper tracts and the prostatic urethra are normal.

### Ongoing Management

#### Question 4:

Recommended treatment at this time would be:

- a. Observation
- b. A 3-week course of BCG
- c. A 6-week course of BCG
- d. A 6-week course of BCG plus interferon
- e. Cystectomy and neobladder

### Discussion

The only incorrect answer to this question is observation. While 3 weeks of BCG would be appropriate in most instances, patients who have not been exposed to BCG for a long time may require more than three instillations to achieve maximal stimulation. The most certain method for effectively stimulating the immune response would be to give a 6-week course of BCG plus interferon. When interferon is added to BCG, it appears to overcome the immune suppression induced by excess BCG. Since this patient has previously responded to BCG, he has a good chance of responding to the combined treatment. Cystectomy would most likely be curative, and should be offered as an option in such patients.

### Conclusion

Optimal management of superficial bladder cancer requires the judicious use of surgery, chemotherapy, and immunotherapy. The decision to press on with intravesical therapy or remove the bladder should be made with the patient’s informed participation. BCG therapy is highly effective, but it can be ineffective if given too frequently or in excessive doses. The combination of intravesical BCG and interferon alfa can provide an effective rescue therapy for patients in whom BCG alone fails.

## References

CME Posttest

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

Original Release Date: April 30, 2001

CME Instructions

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:

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Name ________________________________________________________________________ Credentials ________________

Mailing Address ___________________________________________________________________________________________

City ___________________________________________________________________ State _______ ZIP _______________

Phone #______________________________________________ Fax # ______________________________________________

E-mail ___________________________________________________________________________________________________

Please indicate your answers below (circle one).

1. The initial diagnostic approach for the patient presenting in this case should include:
   a. Upper tract imaging  
   b. Careful resection and biopsy  
   c. Bimanual examination  
   d. All of the above

2. Factors that increase the risk of progression in patients with grade 3 TCC include:
   a. Absence of CIS  
   b. Absence of p53 abnormality  
   c. Vascular invasion  
   d. Single focus of disease

3. Patient risk factors favoring initial combination therapy with intravesical BCG and interferon alfa include:
   a. Physical condition precluding cystectomy  
   b. Invasion beyond the muscularis mucosa  
   c. Tumors less than 3 cm in diameter  
   d. a and b

4. Patients who have had an initial course of BCG often show a suppressed immune response after the fourth, fifth, and sixth instillations during the second course.
   a. True  
   b. False