Intravesical Bacillus Calmette-Guerin for Treating Bladder Cancer

Lee Ann Boyd

Bladder cancer continues to be a leading cause of malignant neoplasm in men. Since 1976, Bacillus Calmette-Guerin (BCG) has been a recommended treatment for superficial bladder malignancy. BCG treatment indications, administration, side effects, patient education, and nursing implications are discussed.

Bladder cancer is the fourth leading cause of malignant neoplasm in men. Over the last 2 decades, the incidence of bladder cancer as well as the mortality rate have been on the rise. The American Cancer Society (ACS, 2003) estimates that there will be 57,400 new cases of bladder cancer diagnosed in 2003 in the United States. The ACS (2003) estimates that there will be 12,500 deaths from bladder cancer in 2003 in the United States. In 1998, the mortality rate from bladder cancer was estimated to be 23% (Cookson & Holzbeierlein, 2000). These disconcerting trends have been the impetus for change in the methods of tumor detection and treatment, in the hopes of preventing disease progression.

In 1976, Morales, Eidinger, and Bruce first documented Bacillus Calmette-Guerin (BCG) to be effective in treating superficial bladder malignancy. As outlined in the following case presentation, BCG remains the standard treatment for carcinoma in situ (Losa, Hurle, & Lembo, 2000). Patients who are at increased risk of tumor progression or recurrence may be candidates for prophylactic BCG intravesical therapy (see Table 1). Other patients may have additive benefits by completing a second induction course of BCG (Dalogne & Herr, 2000). For those who fail BCG therapy or cannot tolerate BCG, medications such as interferon alpha-2B may be added for its synergistic effects and low-toxicity profile (Bird & Soloway, 2002; Cookson & Holzbeierlein, 2000). Alternative therapies for treating bladder cancer include intravesical chemotherapeutic agents, such as mitomycin-C and thiopeta (Cookson & Holzbeierlein, 2000; Kamat & Lamm, 2000).

Case Study

A 62-year-old Caucasian male presents to your clinic with a 3-day history of intermittent, gross painless hematuria. He denies a history of urologic problems. Psychosocial history, however, is positive for a 50-pack/year of smoking.

Urologic evaluation includes an intravenous pyelogram (IVP), which was normal, and a urine cytology suspicious for malignant cells. Cystoscopy reveals a medium-sized, papillary bladder tumor. The patient elects to have a transurethral resection (TUR). The pathology is consistent with Grade III transitional cell carcinoma with focal invasion of the lamina propria.

Once the patient had recovered from the TUR of a bladder tumor, six weekly BCG intravesical treatments were given. Other than local irritative voiding symptoms and a low-grade fever, which occurred after the third BCG treatment, the patient tolerated the treatments well. Followup cystoscopy performed 4 weeks later showed no evidence of recurrent tumor. Maintenance therapy with BCG was subsequently initiated.

Pharmacologic Action

BCG is an attenuated live strain of mycobacterium bovis, the causative organism for tuberculosis. Its exact mechanism of action is not known; however, it is thought to produce a local inflammatory reaction as well as an immunologic response (Kamat & Lamm, 2000).

With the aid of fibronectin, live mycobacteria attach to epithelial cell membranes. The subsequent inflammatory reaction leads to infiltration of surface epithelium with macrophages and CD4 T-lymphocytes. The resultant hypersensitivity reaction potentiates the release of cytokines, including interferon-y, tumor necrosis factor (TNF), and interleukin (IL-1, IL-2, IL-6, IL-8, and IL-10), which appear to be
toxic to cancer cells (Curtis & Soloway, 1998; Greenberg & Ignatoff, 2001).

**Indications**

Intravesical BCG is indicated in the treatment and prophylaxis of high-grade Ta (noninvasive papillary cancer), T1 (invasion of lamina propria), and Tis (carcinoma in situ) of the urinary bladder (Swibold, 1999).

**Dosage and Administration**

The recommended dose and schedule of intravesical BCG therapy varies, and has yet to become standardized (Kamat & Lamm, 2000; Cookson & Holzbauerlein, 2000). For the purpose of this discussion, reference will be made to the Pasteur strain of BCG (TICE® BCG). A 50 mg ampule of intravesical BCG is reconstituted with 50 ml of sterile preservative-free saline in a syringe. The syringe is then gently rotated to mix well. The medication should be instilled intravesically by gravity via urethral catheter using aseptic technique. It is recommended that BCG be stored at 4 degrees C until use, and then administered immediately after reconstitution. The medication is held in the bladder for 2 hours if possible. Retention longer than 2 hours may be of little clinical benefit, and may increase the incidence and severity of irritative voiding symptoms (Hudson, Gerber, & Ratliff, 2000). BCG is usually given weekly for 6 weeks. This initial course may be followed by maintenance therapy at 3, 6, 12, 18, and 24 months. Contraindications of BCG administration are listed in Table 2.

**Nursing Implications**

Health care worker safety is of utmost importance in the handling and administration of BCG, as well as the disposal of BCG-contaminated medical supplies. It is essential the nurses responsible for reconstituting BCG wear eye protection and a mask. Ideally, the mixing of BCG should take place in a biocontainment hood; however, when this is not feasible, a gown should be worn to reduce the risk of BCG contacting with broken skin.

**Table 1.**

<table>
<thead>
<tr>
<th>Risk Factors for Progression or Recurrence of Bladder Cancer</th>
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<tr>
<td>• Multifocal disease</td>
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<td>• Large bladder tumors (&gt;3-5 cm)</td>
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<td>• High-grade tumors</td>
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<tr>
<td>• Dysplasia or carcinoma in situ (CIS) in addition to papillary tumor</td>
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<tr>
<td>• Positive urinary cytology after TUR of bladder tumor</td>
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<tr>
<td>• Previous tumors</td>
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<tr>
<td>• Frequent recurrences</td>
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<td>• Lamina propria invasion</td>
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**Table 2.**

<table>
<thead>
<tr>
<th>Contraindications of BCG</th>
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<tr>
<td>• Do not administer BCG within 14 days of TUR of bladder tumor*</td>
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<tr>
<td>• Acute febrile illness*</td>
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<tr>
<td>• Concurrent UTI*</td>
</tr>
<tr>
<td>• Gross hematuria*</td>
</tr>
<tr>
<td>• Traumatic catheterization*</td>
</tr>
<tr>
<td>• Pediatric use has not been established</td>
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<tr>
<td>• Pregnancy category C</td>
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<tr>
<td>• Active tuberculosis (must be ruled out in PPD-positive individuals)</td>
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<tr>
<td>• Immunosuppressed individuals: May have impaired clinical response to BCG, as well as greater risk of acquiring systemic BCG infection due to:</td>
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<tr>
<td>- disease (for example, leukemia, lymphoma, AIDS)</td>
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<tr>
<td>- cancer treatment (for example, radiation, chemotherapy)</td>
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<td>- immunosuppressive therapy (for example, corticosteroids)</td>
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* Places the patient at increased risk of developing disseminated BCG infection.

Adapted from Curtis & Soloway (1998); Hudson et al. (2000); Organon Inc. (2002).

Intravesical BCG may be postponed for 7 to 14 days if gross hematuria is present or the patient has experienced traumatic catheterization. In male patients who are difficult to catheterize, the patient’s record should note that a coudé catheter is necessary to prevent urethral mucosa injury. BCG is a live, attenuated organism which can cause local or even systemic infection and could ultimately result in sepsis or death. Fortunately, these severe adverse events are rare. More commonly, patients may experience dysuria, frequency, malaise, and possibly hematuria, and/or low-grade fever in accordance with state and federal guidelines. All work surfaces must be disinfected with agents such as chlorine bleach or 70% isopropyl alcohol (Reilly, 1995).

A urinalysis is performed immediately preceding each BCG treatment. Minimal pyuria is to be expected. If pyuria is marked or bacteriuria is present, a culture should be performed and the treatment postponed. If irritative symptoms are persistent at the time of a BCG treatment, that treatment may be postponed for up to 2 weeks (Hudson et al., 2000).

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Intravesical BCG may be postpone-
Low-grade fever may indicate a favorable response to BCG therapy (Curtis & Soloway, 1998). Approximately 50% of patients will experience lower urinary tract symptoms as a result of the medication-induced inflammatory response within the bladder. Typically, side effects are usually observed after the third treatment and may progress after each successive treatment. Symptoms may occur 4 to 6 hours after the treatment and may persist for 24 to 72 hours. Acetaminophen, phenazopyridine, and/or anticholinergics may be given for symptomatic relief (Curtis & Soloway, 1998; Organon, Inc., 2002). A patient developing fever of 101.3 degrees F or greater, symptoms of prostatitis, epididymitis, or orchitis lasting more than 2 to 3 days should be evaluated for active infection. The patient may be hospitalized and BCG discontinued. Infectious disease specialists should be consulted. Treatment generally consists of broad-spectrum antibiotics to cover gram-negative infections. Combination therapy with antimycobacterial drugs such as isoniazid, rifampin, and ethambutol may also be warranted. Pyrazinamide is typically resistant to BCG (Hudson et al., 2000). A patient with systemic infection should be treated for at least 3 to 6 weeks (Bird & Soloway, 2002), while others may be treated with combination therapy with antimycobacterial drugs for up to 3 to 6 months (Hudson et al., 2000).

### Patient Education

Education for patients receiving intravesical BCG therapy is important to ensure compliance with treatment and to minimize complications. Both verbal, and whenever possible, written instructions regarding BCG instillation should be used to enhance patient understanding of information.

Adapted from Hudson et al. (2000); Organon Inc. (2002); Reilly (1995)
Treating Bladder Cancer
continued from page 191

The health care professional explains that BCG is a solution composed of tubercular bacillus that yields an inflammatory response locally to treat bladder cancer, or prevent its recurrence. As it is biologically active, care must be taken to teach patients the proper hygienic measures and cleansing techniques to prevent contamination of others.

The expected side effects associated with an inflammatory response within the bladder are discussed and reassurance given that those symptoms are usually transient. Advise the patient that more serious adverse events such as fever greater than 101.3 degrees F, chills, fatigue, cough, gross hematuria, pain, or flu-like symptoms should be reported to the health care provider (Curtis & Soloway, 1998; Reilly, 1995). Other important points to discuss with the patient are listed in Table 4.

Conclusion

Superficial bladder cancer poses a common problem for urologic practitioners. In those patients with carcinoma in situ or those at risk for progression of bladder cancer, BCG intravesically may reduce the risk of morbidity and mortality associated with bladder cancer. It is imperative that urologic nurses educate patients and stress the importance of followup care, including the need for repeat cystoscopy at regular intervals.

Currently, there are no markers available that predict BCG response (Dalbagné & Herr, 2000). In the future, randomized trials with intravesical BCG may help address the issues of standardization of dosing, as well as the efficacy of maintenance therapy.

References


