Management of Bacillus Calmette-Guérin–Refractory Bladder Cancer: Case Studies

Includes Highlights From a Roundtable Discussion

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STATEMENT OF NEED
About 500,000 people in the United States are currently affected by bladder cancer, making the disease the fourth most common cancer among men and the eleventh most common among women.

About 70% of bladder cancer patients present with superficial, nonmuscle invasive disease. Intravesical administration of bacillus Calmette-Guérin (BCG) following resection of the nonmuscle invasive tumor is the current standard management strategy. Patients with carcinoma in situ (CIS) treated with intravesical BCG have a 60% to 70% chance of a complete and durable response. About 20% of patients discontinue BCG therapy due to local and systemic toxicity, however, and 30% to 40% show evidence of recurrence following treatment. Patients who cannot tolerate BCG therapy or have a tumor recurrence after one or more inductions need careful assessment and consideration of salvage therapies. The therapeutic options include a repeat course of BCG alone, BCG plus interferon, and/or intravesical chemotherapy. For some patients, radical cystectomy may be the best option for long-term disease-free survival. Unfortunately, because of comorbid conditions, the patient may not be clinically suitable for this major surgical procedure or may not be accepting of the surgery's physical and psychological consequences.

Several chemotherapeutic agents are used for intravesical therapy. Gemcitabine has shown efficacy when used systemically against advanced bladder cancers; this has prompted the examination of its use intravesically. Although this form of administration has acceptable safety, its usefulness in the treatment of BCG-refractory CIS is unclear. For patients with BCG-refractory CIS, valrubicin is the only FDA-approved agent for salvage therapy, but response rates are only approximately 20% at 6 months. If a patient does not have a complete response or if CIS recurs, cystectomy must be reconsidered.

In BCG-refractory patients, there is a lack of agreement and clarity among urologists regarding when valrubicin should be offered, or when other clinical options should be considered prior to radical cystectomy. Practicing urologists need to be aware of the full range of treatment options available for this high-risk patient population, who receive little benefit from additional courses of BCG and are either unwilling or inappropriate surgical candidates.

TARGET AUDIENCE
This activity has been designed to meet the educational needs of US-based urologists who treat patients with bladder cancer.

EDUCATIONAL OBJECTIVES
This educational initiative aims to reach urologists, oncologists, and urologic oncologists. At the conclusion of this activity, the participant should be able to:

- Review epidemiology and disease burden of BCG-refractory bladder cancer
- Explain therapeutic options for patients with BCG-refractory bladder cancer

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Management of Bacillus Calmette-Guérin–Refractory Bladder Cancer: Case Studies

To assist urologists in achieving enhanced knowledge in treating bacillus Calmette-Guérin (BCG)—refractory bladder cancer, a panel of experts in this field—Dr. Neal Shore as Chair, with Dr. Sam Chang and Dr. Ashish Kamat—convened to discuss the issues and controversies that arise when treating patients who have failed BCG therapy, and how to determine an optimal course of action. Their discussion and insights involving the management of challenging cases follow after a brief review of the literature.

Introduction

Bladder cancer affects more than 350,000 patients annually worldwide, with 70,000 new cases (approximately 52,000 men and 18,000 women) diagnosed in 2009 in the United States alone [1,2]. The disease typically affects older individuals [2]. Americans have a 2.4% risk of developing this cancer, with men having a risk 3 times higher than that of women [3]. Bladder cancer is the most common urologic type of cancer in men [4] and the eleventh leading cancer in women [2,3]. Caucasian Americans have approximately twice the risk of developing bladder cancer as compared with African Americans, and Latin Americans have a lower risk than do African Americans [3,4]. The reason for these differences is not well understood.

According to the National Cancer Institute Surveillance Epidemiology and End Results (SEER) Registry, there has been a gradual increase in bladder cancer incidence since 1975 [3]; however, despite this rise in incidence, the death rate has been gradually declining [3], most likely due to earlier detection and improved implementation of treatments. More than 14,000 deaths were attributed to bladder cancer in the United States in 2009 [2], and the 5-year relative survival rate (survival of bladder cancer patients in comparison with the general population) for 1999 to 2005 was 80% [3]. The 5-year relative survival rates differ depending on the stage of cancer—97.2% for carcinoma in situ (CIS), 74.3% for localized, 36.2% for regional, 5.8% for distant, and 56% for unstaged [3].

Etiology

There is no single, primary etiologic cause of bladder cancer: environmental as well as genetic factors appear to play a causative role [4]. The link between environmental carcinogens and bladder cancer was first recognized in 1895 by Ludwig Rehn, whose work on bladder tumors correlated an association with aniline dye workers [4,5]. In the 100+ years since Rehn’s research, certain industries, occupations, and chemical agents (eg, aromatic amines used in the dye industry, tobacco usage, and petroleum-based products) have been linked to bladder cancer [4,6]. With the reduction of these types of occupation-related exposures, active smoking has been well established as the most significant environmental risk for bladder cancer, associated with more than half of the diagnoses [6,7]. Active smoking and longer smoking duration are associated with higher risk of bladder cancer versus no smoking or more distant smoking history [8]. Although diet may also play a role in the etiology of bladder cancer, no consistent data linking bladder cancer to intake of certain nutrients or micronutrients have been established [9]. Molecular mechanisms that play a role in bladder cancer include altered metabolism or detoxification of carcinogens and inherent or acquired genetic abnormalities that may promote development of tumors, inhibit tumor suppressor genes, or damage DNA repair enzymes [4].

Approximately 90% of cases of bladder cancer arise from the transitional cells of the bladder mucosal epithelium. Noninvasive, papillary tumors protruding from the mucosal surface may also be present [6]. These tumors, which typically do not invade the bladder wall, are usually amenable to resection but may oftentimes recur, depending upon pathological risk factors [6]. Less common subtypes of bladder cancer include squamous carcinoma in less than 3% of cases and adenocarcinomas in less than 2% of cases [10]. One-third of bladder cancers present as solid, nonpapillary tumors, which may originate from in situ dysplasia and/or CIS [6]. These tumors may invade the bladder wall and thus have an increased risk to metastasize; the 5-year survival rate in patients with any pathologic stage of bladder cancer is only 60% [11].

Update on Diagnosis

The majority of patients with all stages of bladder cancer present with hematuria—either visible (“gross”) or microscopic [4]. Physical examination is often unremarkable, especially in nonmuscle invasive disease; however, transurethral resection of the bladder tumor (TURBT), cystoscopy and biopsy, cytology, and radiologic imaging have been the mainstays of evaluation, diagnosis, and staging [4]. Adjunctive, voided

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<th>Table 1. 2004 WHO Classification of Nonmuscle Invasive Urothelial Neoplasia [4]</th>
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<td>Hyperplasia (flat and papillary)</td>
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<td>Reactive atypia</td>
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<td>Atypia of unknown significance</td>
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<td>Urothelial carcinoma in situ</td>
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<td>Urothelial papilloma</td>
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<td>Papillary urothelial neoplasm of low malignant potential</td>
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<td>Nonmuscle invasive low-grade papillary urothelial carcinoma</td>
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<td>Nonmuscle invasive high-grade papillary urothelial carcinoma</td>
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urinary-based markers have been investigated and utilized to aid in the diagnosis and surveillance of patients with nonmuscle invasive urothelial cancers. The goal of these markers is to improve the efficiency for scheduling cystoscopy and possible biopsy [4].

Since its introduction, TURBT not only assists in the diagnosis of bladder cancer but also provides histologic information for staging and grading of the cancer, which remains an important prognostic indicator for disease recurrence and progression [4]. In 2004, the World Health Organization (WHO) and International Society of Urologic Pathologists revised the consensus classification grading system for papillary cancers that was originally put forth by WHO in 1973. This system has been the most widely used classification system for this disease [12]. Among the revisions is a new category of papillary urothelial neoplasm of low malignant potential and classification of nonmuscle invasive papillary carcinomas as either low or high grade (Table 1) [4,12].

### Common Treatment Practices

Treatment of nonmuscle invasive bladder cancer is typically initiated with careful cystoscopic examination of the bladder and urethra followed by TURBT, which provides tissue specimens for information regarding tumor type, grade, and depth of invasion (stage) [4]. Following resection of all visible tumors, or in cases of CIS where diffuse tumors prevent complete resection, urologists may opt for perioperative or postoperative adjuvant intravesical immunotherapy or chemotherapy to prevent recurrence.

Photoagony therapy and laser ablation may be considered as secondary treatments, depending on the tumor location and grade [4]. For low-risk and recurrent nonmuscle invasive papillary bladder tumors, office fulguration or cystologic surveillance may suffice [13].

Intravesical therapy for nonmuscle invasive bladder cancer is a common practice [4,14]. Agents can be administered intravesically as an adjuvant treatment or as part of a maintenance therapy protocol to prevent recurrence [4]. Immediate perioperative administration post-TURBT theoretically destroys residual microscopic tumors and circulating cells to prevent reimplantation at the time of surgery [4,14]. In maintenance therapy, intravesical administration provides long-term immunostimulation and/or chemotoxicity to prevent disease recurrence [15].

### Bacillus Calmette-Guérin

Bacillus Calmette-Guérin (BCG) is the most commonly used intravesical agent for the treatment of nonmuscle invasive bladder cancer and is the first-line treatment for bladder CIS [4]; however, about 20% of patients discontinue BCG due to local and systemic side effects, and recurrence of disease may occur [16]. Up to 40% of patients treated with intravesical BCG following resection of nonmuscle invasive bladder tumor will fail therapy within the first year [17,18]. Salvage therapy of intravesical BCG induction plus maintenance results in a 15% to 20% response rate after the first year [18]. Combining BCG with interferon allows 60% of BCG-naïve patients to remain disease-free over a 3-year follow-up period; however, patients who fail more than 1 induction with BCG alone prior to receiving BCG plus interferon are 2 to 3 times more likely not to respond to the adjuvant therapy (P ≤ .0001) [19]. Bladder cancer has been cited as a uniquely costly cancer in relation to the annual US expenditure for oncologic cancers, largely due to its treatment recurrences and surveillance [20]. Medicare payments for individuals with bladder cancer total $57,629 from diagnosis to death—the highest of 5 common cancers [21].

Patients who fail BCG therapy for CIS, or who have a tumor recurrence after the second induction, do not respond to BCG alone at a higher rate [22]. Treatment is then aimed at preventing progression, including recurrences, and requires maintenance therapy [22].

### BCG-Refractory Patients

According to Martin and Kamat, “any recurrence of tumor after BCG therapy can be defined as BCG failure; however, not all failures under this definition have the same prognosis. From a practical standpoint, relapse is considered recurrence of tumor after a period of disease-free status; here, the tumor responds to initial BCG treatment, but the patient develops another tumor after some time without disease. The disease-free interval is a prognostic variable and indicates that patients with a late relapse (more than 2 years) may benefit from repeated BCG, while early-relapsing (less than 1 year) patients are more likely to progress. Disease is defined as BCG refractory if there is persistent disease despite 6 months of initial BCG therapy (which may include either maintenance or re-treatment at 3 months secondary to persistent or recurrent disease). This category includes any progression in stage or grade by 3 months after the first cycle of BCG” [18]. For CIS, the time point at which a patient is considered to have “failed” BCG is the 6-month evaluation—not the 3-month evaluation, as is the case for papillary disease.

Therapeutic options for patients with CIS who fail BCG therapy include intravesical chemotherapy (eg, gemcitabine, valrubicin, etc), photodynamic therapy, and hyperthermia. Table 2 illustrates some therapeutic options for patients who fail BCG therapy.

**Table 2. Treatment Options for Failed Bacillus Calmette-Guérin (BCG) Therapy**

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<th>Chemotherapeutics</th>
<th>Immunomodulators</th>
<th>Biological Agents</th>
<th>Other</th>
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<tbody>
<tr>
<td>Gemcitabine</td>
<td>Interferon</td>
<td>Mycobacterial Cell Wall Extract (MCWE)</td>
<td>Cystectomy</td>
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<td>Valrubicin</td>
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<td>Hyperthermia</td>
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<td>Docetaxel</td>
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<td>Mitomycin C</td>
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and docetaxel), immunotherapy, mycobacterial cell wall preparation, hyperthermia, photodynamic therapy, liposomes, and gene therapy (Table 2).

(Note: All treatment options discussed in the following section are nonlabeled, non-FDA approved, and/or experimental, with the exception of valrubicin.) For some patients, radical cystectomy may be the best option for long-term disease-free survival, but some patients are either poor candidates for radical surgery due to comorbid conditions or may not accept the quality-of-life consequences from the morbidity of bladder removal, especially if other therapeutic options are available.

CHEMOTHERAPEUTICS

Chemotherapeutic agents used for salvage intravesical therapy for BCG-refractory CIS include gemcitabine and valrubicin. Valrubicin* is the only FDA-approved agent for the treatment of BCG-refractory CIS (Table 3) [8]. Gemcitabine is effective when used systemically against advanced bladder cancers [19], and this has prompted the examination of its use intravesically. The intravesical use of gemcitabine has demonstrated an acceptable safety profile due to its minimal toxicity [22], but its usefulness in the treatment of BCG-refractory CIS is unclear. In an open-label trial including 40 BCG-refractory patients with noninvasive Ta, T1, and/or CIS bladder cancer, weekly instillations of gemcitabine for 6 weeks resulted in complete remission in 18 out of 24 (75%) intermediate-risk BCG-refractory patients and 7 out of 16 (43.7%) high-risk BCG-refractory patients [19,23]. In a phase 2 trial consisting of twice-weekly administration of gemcitabine in 30 BCG-refractory patients, 50% of patients experienced a complete response to therapy, with a median follow-up of 19 months, but 40% of patients experienced recurrence, with a median recurrence-free survival of 3.6 months. Eleven of the 30 patients eventually proceeded to radical cystectomy [24].

For patients with CIS and failed BCG therapy, valrubicin has been an option for more than 10 years. It is indicated for intravesical therapy in patients for whom immediate cystectomy would be associated with unacceptable morbidity or mortality. In a study of 90 patients with recurrent CIS in whom multiple prior courses of intravesical therapy failed, including at least 1 course of BCG, 19 patients (21%) had a complete response with 6 weekly instillations of intravesical valrubicin [25]. Seven patients of these 19 remained disease free at the last evaluation, with a median follow-up of 30 months. Complete response was defined as no evidence of disease recurrence for 6 months or longer. In addition, 14 patients who did not meet the strict study definition of a complete response had superficial Ta disease only. Most side effects were mild, with only 3 patients in the study unable to receive the 6 scheduled doses due to tolerability issues [19]. A retrospective analysis in the 16 patients with complete responses demonstrated that time to recurrence of their disease after treatment with valrubicin was longer than the time to recurrence after previous courses of intravesical therapy [26]. Recurrence was eventually documented in 79 patients, 2 of whom had disease progression to stage T2. Of these 79 patients, 44 (56%) eventually underwent cystectomy. In patients with BCG-refractory CIS, delaying cystectomy for 3 months to assess the effect of valrubicin did not appear to pose undue risk [25]. Importantly, strict surveillance for these patients is required in order to best decide upon subsequent surgical options if the disease progresses or is nonresponsive to valrubicin therapy.

Docetaxel, which has an established clinical history in treating prostate, breast, ovarian, and non-small cell lung cancer, has been recently investigated in the management of nonmuscle invasive bladder cancer refractory to BCG [27]. Twenty of 33 patients (61%) had a complete response after 6 weekly induction treatments. Eleven of the patients with a complete response continued with maintenance therapy—10 received docetaxel and 1 received BCG plus interferon. About one-third of the patients experienced grade 1 or 2 local toxicities. One- and 2-year recurrence-free survival rates were 45% and 32%, respectively, based on a median follow-up of 29 months. Long-term studies, with a median follow-up of 4 years, reported a complete disease-free response in 22% (4 of 18) of patients, a partial response (defined as a single recurrence with no further therapy) in 17% of patients, and failure in 61% of patients. The median disease-free survival time was 13.3 months [28].

A phase 2 trial evaluating a doxorubicin analogue, AD32, in patients with recurrent or refractory CIS who failed prior BCG therapy found that 28 of 42 patients (67%) remained alive after a median follow-up of 61.1 months [29]. AD32 was administered intravesically in 6 weekly doses. Recurrence-free rates at 12 and 24 months were 20% and 15%, respectively, for patients with transitional cell carcinoma and 80% at both time periods for CIS patients with a complete response. Infection was the most common treatment-related toxicity, and increased frequency/urgency was the most common genitourinary-specific toxicity.

Suramin, an antitrypanosomal agent with antineoplastic activity and serious systemic side effects, has been evaluated for its potential use as an intravesical agent in patients with a history of recurrent superficial bladder cancer. Phase 1 trials conducted by Ord and colleagues established an intravesical dose with lack of toxicity and low systemic

| Table 3. Intravesical Chemotherapy for Nonmuscle Invasive Bladder Cancer [4] |
|---------------------------------|---------------------------------|
| Gemcitabine                     | Deoxycytidine analog; inhibits DNA synthesis |
| Valrubicin, doxorubicin, epirubicin | Intercalating agents; inhibit DNA synthesis |
| Mitomycin C                     | Antibiotic; inhibits DNA synthesis |
| Thiotepa                        | Alkylating agent; crosslinks nucleic acids |


IMMUNOMODULATORS

Adjuvant therapy with BCG and interferon-alpha has been studied in BCG-refractory patients. In a national multicenter phase 2 trial, patients with superficial bladder cancer who had previously failed BCG therapy were treated with a reduced dose of BCG plus interferon-alpha (50 million units) [31]. After induction therapy, those who were relapsed received a 3-week course of reduced-dose BCG plus interferon-alpha at 3, 9, and 15 months. In 467 patients who had previously failed BCG therapy, 45% remained disease free at a 24-month median follow-up. Statistically significant risk factors for recurrence were identified as more than 1 prior BCG failure, stage T1, tumor size > 5 cm, and multifocality. Thus, in those patients at highest risk for recurrence and progression, the combination of BCG with interferon is least likely to be effective and, as a result, puts in question its usefulness.

BIOLOGICAL AGENTS

In an attempt to find a better tolerated intravesical agent for CIS with the efficacy of BCG but without the undesirable side effects and toxicity of traditional BCG, Morales and colleagues investigated a mycobacterial cell wall extract (MCC) from Mycobacterium phlei, which does not contain live organisms [32]. MCC is a sterile mycobacterial cell wall-DNA complex with 2 modes of action—immune stimulation and direct antican- cer activity [33]. An early study examined 61 patients with CIS and treated with intravesical MCC once a week for 6 weeks and then monthly for 1 year [32]. Kaplan-Meier estimates demonstrated negative cystoscopy and biopsies in 62.5% of patients at 12 weeks, 49.3% of patients at 24 weeks, and 41.1% of patients at 60 weeks. Number of responders remained stable after the 60-week point. Patients experienced excellent tolerability with minimal toxicity.

When MCC was administered to 55 patients who previously failed BCG therapy (except for 8 who were BCG naive and 2 who received chemotherapy), complete response at 12 and 26 weeks was 46.4% [34]. These patients received 6 weekly instillations of 8 mg MCC followed by 3 weekly instillations at 12 and 24 weeks. Overall, 90% of all adverse events were mild to moderate in severity, and the agent was well tolerated by patients.

These encouraging results have led to an FDA-approved and fast track open-label clinical trial evaluating MCC in 105 patients with BCG-refractory, unresponsive, non-muscle invasive bladder cancer from 31 urology centers across North America. Patient recruitment was completed in March 2009 [35] and results are expected to be available in mid-2010.

FURTHER TREATMENT OPTIONS

Other efforts to treat patients who have failed BCG therapy include hyperthermia, photodynamic therapy, liposomes, and gene therapy.

Nativ and coworkers investigated mitomycin C instillation followed by bladder wall hyperthermia to 42°C in 111 patients with prior failed BCG therapy [36]. This trial resulted in an estimated disease-free survival of 85% and 56% after 1 and 2 years, respectively. Maintenance therapy was associated with a lower recurrence—39% at 2 years versus 61% for no maintenance (P = .01). Photodynamic therapy with porfimer sodium has produced overall response rates of 84.2% in 19 patients with recurrent superficial papillary transitional cell carcinoma and 80% in 20 patients with refractory CIS [37]. Photodynamic therapy following oral administration of 5-aminolevulinic acid has also produced encouraging results in rapidly recurring, multifocal, BCG-refractory superficial transitional cell carcinoma and CIS [38].

BC-819, a DNA plasmid that contains the H19 gene regulatory sequences that control expression of an intracellular toxin, was administered intravesically for 7 weeks in 18 patients with prior BCG failure and low-grade superficial bladder cancer that expressed H19 [39]. Patients who responded continued to receive BC-819 once monthly for 1 year. This treatment resulted in complete ablation of the marker tumor without any new tumors in 22% of the patients. Nearly half of the patients (44%) had a complete tumor ablation or a 50% reduction of the marker lesion. The most frequent adverse events were mild to moderate bladder discomfort, dysuria, and micturition urgency, among others.

CYSTECTOMY

Since 8 out of 10 high-risk patients with bladder cancer who are not cancer-free 3 months after BCG therapy may be expected to experience disease progression [40], cystectomy becomes an appropriate option for these patients. Radical cystectomy is successful and tolerated, even in patients older than 75 years [41]. Elderly patients with Karnofsky performance status of 80, however, have almost twice the risk of sudden death than patients with a score of 90 or greater [41].

Once BCG-refractory disease status has been identified, timely cystectomy currently offers the best long-term disease-free survival [4]. Patients who received cystectomy for recurrent, high-risk, nonmuscle invasive transitional cell carcinoma less than 24 months after TURBT and initial BCG therapy had a significantly better 15-year survival than those who had the surgery after 24 months of follow-up [42]. For this reason, AUA guidelines recommend cystectomy as the preferred treatment option in patients with high-risk disease who failed initial intravesical therapy [4]. The recent discovery of several bladder cancer tumor urinary and serum markers has the potential to assist urologists in tailoring surveillance strategies to individual patients and, in the future, may be used to predict BCG failures. Patients testing positive for these markers could be offered cystectomy or other therapies with more propitious timing [43].

FUTURE DIRECTIONS

Although a number of studies have been conducted and published describing various treatment options for cases of BCG failures, there is a lack of consensus among urologists regarding the point of failure and when to advance treatment among BCG-refractory patients. When treatment is advanced, what therapy will produce the most successful outcome? What criteria should be used to select the next treatment option? These questions remain unanswered and are the focus of future investigations in BCG-refractory bladder cancer.
**Dr. Shore:** Let us begin by asking, how do you define “BCG-refractory disease” for the urology resident?

**Dr. Chang:** I use the term BCG failure as a catchall phrase, and the question then becomes in which particular situation is the patient? Dr. Kamat and others have attempted to categorize patients into groups depending upon what their initial tolerances and responses to BCG were and the time period in which they had disease—still viable, ongoing disease versus a disease-free state with return of disease after completion of BCG therapy. There are different forms and different definitions. Clearly, the patients who are at highest risk are those who after an initial induction course of BCG (6 weeks of BCG therapy followed by an evaluation 6 weeks after the last induction) still have disease. A subgroup of these patients will respond with time alone [18], but there will be patients who require additional courses of BCG therapy to show a response [14] and those who will not respond. Defining BCG failure then depends on a patient’s initial response and what happens afterwards.

**Dr. Kamat:** Essentially, patients treated with BCG will either respond or not respond. By definition, those who do not respond are considered BCG failures. It is important to distinguish whether failure is due to the inability of the patient to tolerate therapy (eg, infection, intolerance) or due to tumor recurrence or persistent disease. If a tumor does not respond to BCG, then it is refractory. Relapse can also occur after successful therapy—either soon after treatment or later on. In the latter case, patients will respond similarly to BCG-naive patients if retreated.

Data suggest that for pure CIS, the 6-month time period is when you can say a patient has failed BCG or not, while for papillary disease, it is at about the 3-month evaluation.

**Dr. Chang:** An important significant predictive factor for ultimate BCG failure for me is still the first evaluation at 6 weeks following the last induction. I perform this cystoscopy in the operating room under anesthesia rather than in the office, because it is difficult to distinguish erythema from persistent CIS. I routinely obtain a biopsy and evaluate the patient’s cytolgies. If there is improvement, then I do not think it necessary to pursue cystectomy. If disease is present, the nature of the disease influences my discussion, and I would talk with the patient about the possibility of more BCG, cystectomy, and/or possibly other intravesical options.

**Dr. Kamat:** In my practice, we do not routinely biopsy patients at 3-month intervals. I am very comfortable relying on fluorescence in situ hybridization (FISH) or on cytology to tell me if the red spot I am seeing is a high-grade lesion (ie, CIS) or if it is BCG cystitis. However, if a patient has T1 disease, then I will take him or her to the operating room, because I want to rule out a deeper invasion. Furthermore, while it might be interesting to clarify (with urinary markers) whether a “red spot” is CIS, most patients with CIS at 3 months could be treated with additional BCG rather than being prematurely labeled as BCG failure.

**Dr. Shore:** There exists uncertainty regarding the number of 6-week BCG inductions a patient should receive before deciding that another option should be considered, whether it is for nonmuscle invasive bladder cancer or for CIS. How should we decide?

**Dr. Chang:** It depends on the patient and how many times he or she has been treated. Patients may continue to have disease after an initial 6-week course. Do you repeat the 6 weekly inductions or try 3 weeks instead, and then follow with a maintenance-type regimen? There have been no head-to-head studies to compare these regimens. I will tailor therapy depending upon the patient. If after that initial regimen of BCG or after additional BCG, be it another 6-week induction or 3-week maintenance type dose, a patient still has either CIS or high-grade noninvasive disease, then I am reluctant to try other intravesical therapies if the patient is a candidate for a cystectomy. Patients who fail an initial 6-week course and who want to be aggressive and are fit for cystectomy should consider this option, and I discuss this with these patients. Now if someone who has had BCG a few years ago and has recurrent disease say after 2 years, I would try another 6-week induction course.

**Dr. Kamat:** We sometimes forget that BCG is an immune stimulant and that the T-cells need to be primed to release the appropriate cytokines that exert an effect in the bladder. If disease recurs, it may be because the individual has not been exposed to BCG in a while. This patient will often respond to additional courses of BCG.

Studies examining 6 weeks of BCG induction followed by maintenance every 3 months (reported by Hudson [44]) or monthly maintenance (reported by Balam et al [45]) or even repeated 6 weeks of BCG at 6-month intervals (reported by Palou [46]) showed that the additional instillations of BCG beyond 6 weeks were not better than the 6 weeks alone. Therefore, they concluded that a 6-week induction is adequate. On the other hand, Lamm and coworkers found that a 6-week induction course plus 3 weeks of maintenance therapy has some benefit [15]. Andres Bohle reported that levels of cytokines increase with each instillation over 6 weeks [47]. Waiting 6 weeks and repeating 6 weeks of BCG instillation leads to increases in levels of cytokines at weeks 1, 2, and 3, but in a majority of patients, cytokine release is suppressed at weeks 4, 5, and 6. Couple these data with those of Lamm, and it seems that 3 weeks of maintenance is ideal.

**Dr. Chang:** When reviewing the data for intravesical immunotherapy and chemotheraphy, the regimens that people have published are quite variant—from once a week to once a month, to 2 cycles over 3 months, to alternating types of therapy—it’s all over the place. When these studies, however, are grouped into induction-only regimens versus induction plus maintenance regimens, recurrence rates are universally lower in those regimens that have some form of maintenance, regardless of the actual maintenance regimen. Unfortunately, there are tradeoffs, including cost, inconvenience, and side effects.
**Dr. Shore:** When do you feel justified in recommending maintenance therapy, and how does that compare with current AUA guidelines?

**Dr. Kamat:** Not every patient needs maintenance therapy. There are some who do well and some who do not. Results from a recent study found that a minimum of 1 year of maintenance BCG (3 weekly treatments at 3 months and 6 months following a 6-week induction) is required to significantly affect the recurrence rate [48]. More cycles resulted in further improvement, but the benefits may be outweighed by increased side effects in some patients.

**Dr. Chang:** Unfortunately, the AUA guidelines are vague regarding recommendations in terms of evaluation and follow-up. The AUA guidelines are also vague on what biomarkers we should use, either at the time of diagnosis or at the time of follow-up, and so I think Dr. Kamat’s study regarding the efficacy of the FISH test is going to be important.

**Dr. Shore:** What about the patient, who over a period of at least 6 months, has failed BCG therapy and has persistent CIS? Are all patients appropriate for radical cystectomy at this point?

**Dr. Chang:** The standard of care would be to proceed with cystectomy, but we need to determine whether or not the patient is truly a candidate for this surgical procedure. We have found that office evaluation and performance status give us a good indication but are clearly far from perfect. There are many patients for whom cystectomy would be the most effective treatment of choice, but weighing the advantages and disadvantages leads the physician and/or the patients to consider some other intravesical therapy, such as gemcitabine or valrubicin, since it is now available again.

**Dr. Kamat:** It is important to get patients thinking about radical surgery early on. When I start patients with CIS on BCG, I tell them that if the disease is recurrent or persistent at 6 months, then we will consider cystectomy. This approach allows patients to start thinking about surgery and decreases further delay on their part. If a patient decides against surgery and wants to try another therapy, I tell them that any other available agent has about an 18% to 20% response rate. I am willing to try it, as long as the patient understands that cystectomy is the primary recommendation and is the only one with a proven durable cure rate.

**Dr. Shore:** Strict surveillance is absolutely essential in these patients because they potentially have a very life-threatening disease, but at the same time, they tend to be elderly and frequently have significant comorbidities. Cystectomy is a major procedure with the potential for significant postoperative morbidity and mortality. How do you counsel elderly patients regarding cystectomy?

**Dr. Chang:** It is a mutual decision that many times can be difficult to make. I tell them all the varied risks and that we have a 35% complication rate, most of them minor, but major complications can and do occur. I also tell them that there is a 1% to 2% percent chance of dying and that they will lose an average of 20 to 30 pounds following the procedure. I do say that I expect patients to do everything they were capable of doing before the operation, after this operation.

We as physicians can help guide how the patients choose, and those decisions can be very difficult.

**Dr. Kamat:** The fact remains that radical cystectomy is a major surgery and many patients will experience some complication. However, it is important to emphasize that if they are avoiding cystectomy solely because of the risk of complications, they are only going to get older and that we do not have durable therapy; this means that they will ultimately have to undergo the surgery when they are less able to recover from it because of advancing age.

**Dr. Shore:** What are the nonsurgical options for patients who are candidates for cystectomy, and how does external beam radiation therapy fit into our treatment strategies?

**Dr. Chang:** If patients are set against cystectomy, clinical trials are an option, as is valrubicin. I have never recommended external beam radiation therapy to patients with CIS or noninvasive disease. My biggest concern is that many of these patients have significant lower urinary tract symptoms, which would be exacerbated by external beam radiation therapy. I have used a combination of systemic chemotherapy and radiation therapy on patients with muscle invasive disease, but this is quite infrequent in our practice.

**Dr. Kamat:** I would use intravesical therapy with valrubicin over radiation. Radiation makes it difficult to discern what is going on in the bladder as far as CIS and radiation cystitis are concerned. Furthermore, there are no data that demonstrate that radiation is even effective in this subtype of patients.

A study by Weiss et al looked at a small cohort of 84 patients with high-grade lamina propria–invading tumors who were treated with radical TURBT and adjuvant radiation-sensitizing chemotherapy plus radiation to the pelvic nodes and the whole bladder [49]. The authors were able to show a 71% survival rate if a policy of immediate cystectomy for recurrence or progression was incorporated into the algorithm. If these results are validated by other centers, it would be an important addition to the treatment choices available to our patients.
The following cases discussed by the faculty provide practical insights into bladder cancer management considerations.

**Case 1: Elderly patient with microscopic hematuria**

**HISTORY**
N.S. is a 79-year-old retired construction foreman who initially presented with asymptomatic microscopic hematuria. He cannot recount any specific industrial exposures and has smoked on/off (cigars and cigarettes) for 40 years. He awakens 2 to 3 times per night to void and notes an acceptable force of stream. Outpatient cystoscopy revealed discrete erythematous, velvety areas along the posterior and left lateral aspects of the bladder wall.

**MEDICAL HISTORY**
- Hypertension
- Emphysema
- Hypercholesterolemia
- Type II diabetes
- Myocardial infarction (2007)

**SURGICAL HISTORY**
- Bilateral inguinal hernia repair with mesh
- Appendectomy

**MEDICATIONS**
- Atenolol
- Furosemide
- Glyburide
- Baby aspirin
- Atorvastatin
- Niacin extended-release tablets
- Albuterol inhaler

**LABORATORY VALUES**
- Creatinine: 1.9 mg/dL
- Complete blood count and liver function tests: normal

**UROLOGIC OPERATIONS**
- TURBT (April 2009)
- Pathology reveals CIS in multiple areas, including the posterior wall and left lateral wall
- There is no evidence of lamina propria or muscle invasion
- Cystoscopically obtained bladder washings (cytology/FISH) are positive for malignancy

**UPPER TRACT AND EXTENT OF DISEASE EVALUATION**
- Computed tomography (CT) of chest, abdomen, and pelvis with/without contrast: demonstrated neither extravesical extension mass nor any adenopathy
- Upper tracts are normal

**ADJUVANT THERAPY**
- Induction course full-strength BCG for 6 weeks in May 2009
- Tolerable frequency, urgency, and occasional myalgias, which slightly increased by the fifth and sixth treatments

**FOLLOW-UP TURBT**
- August 2009: demonstrates persistent erythematous, velvety area along base and new areas near trigone. Biopsies reveal persistent CIS without lamina propria or muscle invasion. Undergoes a second 6-week course of induction plus maintenance with BCG at full strength, with similar tolerability
- October 2009: repeat TURBT at similar suspicious site reveals persistent CIS

**OPTIONS/DECISION**
The patient and extended family had a lengthy discussion with their urologist regarding ongoing options. Radical cystoprostatectomy was reviewed, inclusive of all options of diversion as well as open and robotic approaches. Patient would be a difficult candidate for cystectomy because of the multiple comorbidities. Intravesical therapy with valrubcin, 800 mg, once weekly for 6 weeks was discussed, as well as options for non–FDA-approved intravesical agents and clinical trials. Patient and family chose valrubcin intravesical therapy and a protocol of regular surveillance cystoscopy/biopsy with urinary markers. Patient has been followed for 4 months, and there is no evidence of recurrent disease based on biopsies and cytologies.

**EXPERT INSIGHT**
Faculty agreed that valrubcin was an appropriate option for this patient. Dr. Kamat pointed out that although 3-month intervals for cystoscopy and cytology are common, this interval could be stretched if the treatment plan would not change with the findings. Dr. Shore agreed, “... why get the information if you do not know what you are going to do with it?” Dr. Chang added that he wouldn’t hesitate to reintroduce valrubcin down the line if the disease recurred, and perhaps use it in maintenance therapy should the patient tolerate it well. However, he acknowledged that the use of valrubcin in maintenance therapy is off label and that there are no studies supporting its use in this manner.

Although urologists practice off-label use of pharmaceutical agents, it is important for physicians to avoid exposing patients to undue financial risk of nonapproved products and determine ahead of time that the protocol will be reimbursed appropriately. Approaching the manufacturer for assistance and offering patients the opportunity to participate in clinical trials are two options of which the faculty has taken advantage.
Case 2: Patient with microscopic hematuria

HISTORY
S.C. is a 68-year-old active man who initially presented with asymptomatic microscopic hematuria. He has never had gross hematuria and has not had any recent trauma. He is a 50+ pack per year smoker who quit smoking several years ago. He has had some mild urinary hesitancy but has never had retention. He underwent an in-office cystoscopy that revealed suspicious eryhematos areas within the bladder; he then underwent the treatment and evaluation outlined below.

MEDICAL HISTORY
Hypertension
Arthritis

SURGICAL HISTORY
Cholecystectomy

MEDICATIONS
Atenolol
Simvastatin
Baby aspirin

LABORATORY VALUES
Liver function test: normal
Creatinine: 1.0 mg/dL
Prostate-specific antigen: 3.2 ng/mL

UROLOGIC OPERATIONS
• TURBT (March 2009)
• Pathology revealed CIS in multiple areas, including the trigone, posterior wall, and right lateral wall
• No evidence of invasion
• Intraoperative cytology was positive

UPPER TRACT AND METASTATIC STUDIES
• Chest x-ray (April 2009): no evidence of metastatic disease and is consistent with mild chronic obstructive pulmonary disease (COPD) appearance
• Computed tomography (CT) scan of the abdomen and pelvis in April 2009: 3-cm intracranial abdominal aortic aneurysm, no hydronephrosis, and no lymphadenopathy

ADJUVANT THERAPY
• Induction course of BCG: weekly instillations for 6 weeks with full dose of BCG starting in April 2009
• Mild lower urinary tract symptoms were encountered but no systemic complaints

FOLLOW-UP TURBT
• July 2009: persistent areas of erythema are a concern
• Biopsies retaken of areas that are confirmed CIS

OUTCOME
Had a long and thorough discussion with the patient. Options discussed included:
• BCG: either another full induction course of 6 weeks’ duration or a shorter 3-week course of BCG
• Continued surveillance with a follow-up evaluation in several months to see if there is improvement with time (small percentage of patients will experience a delayed response after initial therapy) [19]
• Other intravesical therapies, including valrubicin, gemcitabine, and clinical trials
• Radical cystectomy

OPTIONS/DECISION
The patient opted for radical cystectomy based on the procedure’s success rate for cure, his overall health at that time, and his concern that other treatments might simply delay the inevitable and decrease his chances for a cure. He was aware of the potential comorbidities associated with the surgery. He underwent radical cystectomy with orthotopic neobladder creation. His final pathology does reveal multiple area of CIS; however, his margins and lymph nodes are negative.

EXPERT INSIGHT
This patient elected radical cystectomy; however, most younger patients inquire about alternative therapies that would spare their bladders. Dr. Kamat stated that he would offer the patient another course of BCG therapy and wait 6 months before deciding on cystectomy. Continuation of intravesical instillations beyond 6 months not only adds to the cost of treatment, but these treatments do not have the long-term durable response that cystectomy has, which is important for the younger patient.

The issue of sexual function and quality of life after cystectomy is a concern for many young patients facing this surgery. Dr. Kamat has a few patients who are willing to discuss their history of bladder cancer and cystectomy with others facing a similar situation, and he often asks them to speak to his other patients. He refers other patients to them. Dr. Chang pointed out that prolonging the time to cystectomy puts the patient at risk for disease progression to invasive or metastatic disease, which is no longer curable with cystectomy. Dr. Shore stressed that rigorous surveillance is very important in monitoring these patients during continued intravesical instillations. If these instillations fail, the patient should be aware that cystectomy is the appropriate option.
Case 3: Patient with bladder cancer presents for consultation

HISTORY OF PRESENT ILLNESS
A.K. is a 75-year-old man with a history of bladder cancer, who presents for consultation and recommended treatment

The patient was diagnosed in January 2006 with a high-grade T1 tumor, 1 cm in size, located at the left lateral wall. His urologist discussed options with him and began BCG induction. The patient tolerated the first 5 instillations well, but at the sixth instillation he had (from his recollection) a difficult catheterization. That evening he developed high fevers and severe arthralgia. He recalled being treated with antibiotics for 30 days and reports no current sequelae, but he did not receive any further BCG.

According to a written report from the urologist, the patient had regular surveillance every 3 months and was disease free until March 2007 when he developed a recurrent tumor (about 15 months after first tumor). Tumor was resected and found to be a TaHG tumor (about 15 months later with TaHG after one induction). November 2006: left inguinal hernia repair with mesh. One additional area of erythema was observed on microanalysis. Dr. Kamat, urologist discussed options with him and began BCG induction. Therapy was started at one-third the dose with levofloxacin 6 hours later.

Dr. Chang agreed and stated that he performed an office microscopy to confirm that there are no significant bacteria present before instrumentation for the instillation. Dr. Chang treats low-grade fevers and systemic complaints with nonsteroidal anti-inflammatory drugs or acetaminophen, and significant lower urinary tract symptoms with a reduced BCG dose. Studies have shown that dose reduction results in equivalent recurrence rates as full dose but with improved symptomatology [50]. To help with side effects, Dr. Kamat prescribes a quinolone to be taken 6 hours after BCG instillation and has experienced a significant reduction in the number of phone calls to the office regarding side effects. It is imperative not to administer quinolones before the instillation because they may impede the BCG effects, which will interfere with the immunotherapy.

Dr. Shore shared his practice of performing an office microscopy to confirm that there are no significant bacteria present before instrumentation for the instillation. Dr. Chang agreed and stated that he performs cultures only on patients who have significant symptomatology or if bacteria are observed on microanalysis. Dr. Kamat, on the other hand, does not use any of these tests in asymptomatic patients. He advocates using microscopy only on those patients who are symptomatic. All 3 agreed that they continue with the BCG instillation if they find microscopic hematuria or microscopic pyuria, as long as the patient is not symptomatic and there are no bacteria present on microscopy. Unfortunately, many practices will delay instillation in this scenario, which may not be in the best interest of the patient.

Review of Symptoms
- Recent onset of cough and laryngitis for which he is being treated and is improving
- 12-point review of symptoms is noncontributory
- Nocturia × 2; otherwise genitourinary is negative

Medical History
- Bladder cancer as above
- Hypercholesterolemia
- Hypertension

Surgical History
- Left hip replacement
- July 2005: atrial ablation
- November 2006: left inguinal hernia repair with mesh

Family History
Denies history of prostate cancer or bladder cancer

Social History
- Past smoker: 35-year pack-per-day smoking history; quit when he was in his 50s
- Occasional alcohol use
- Retired army colonel

Allergies
- Erythromycin (tingling)

Medications
- Atorvastatin 20 mg daily
- Multivitamins

Physical Examination
- All age appropriate and within normal limits
- Abdomen with scar of surgery; no costovertebral angle tenderness; no supra-pubic fullness
- Genitourinary: normal male phallus
- Nocturia × 2; otherwise genitourinary is negative
- Prostate: 45 g; no palpable abnormalities

Laboratory Values
- All normal
- Creatinine: 1.1 mg/dL

Impression
History of T1HG tumor, with recurrence 15 months later with TaHG after one induction course of BCG

Subsequent Course
Patient underwent repeat cystoscopy 4 weeks after his recurrent tumor was detected. Prior resection site was seen and re-resection was performed. One additional area of erythema seen near dome, and biopsy was taken. Pathology included granulomatous reactive tissue, but no tumor noted in either biopsy.

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Patient was counseled on the significance of the findings. The BCG failure with specific reference to his time course, as well as the fact that he had only received induction and not maintenance therapy, were discussed, as were various options, including radical cystectomy, intravesical chemotherapy, and repeat immunotherapy with BCG.

Patient elected to pursue BCG re-induction. Therapy was started at one-third the dose with levofloxacin 6 hours later. Patient did well with all 6 instillations. Cystoscopy at 3 months revealed no evidence of recurrence. Patient was placed on maintenance therapy consisting of 3 weekly BCG instillations. He developed a fever lasting 4 hours after the second instillation (self-limiting). For the third instillation, BCG was reduced to one-tenth the dose.

The 6-month evaluation was negative for recurrence (including cytology). Patient was maintained on weekly BCG at one-tenth the dose for 3 weeks, every 6 months.

Currently, at 2 years and 6 months, there is no evidence of disease. Patient is nearing the end of his prescribed 3-year course of BCG with no complaints.

Expert Insight
Faculty agreed that managing symptoms associated with BCG instillations is important. Dr. Chang treats low-grade fevers and systemic complaints with nonsteroidal anti-inflammatory drugs or acetaminophen, and significant lower urinary tract symptoms with a reduced BCG dose. Studies have shown that dose reduction results in equivalent recurrence rates as full dose but with improved symptomatology [50]. To help with side effects, Dr. Kamat prescribes a quinolone to be taken 6 hours after BCG instillation and has experienced a significant reduction in the number of phone calls to the office regarding side effects. It is imperative not to administer quinolones before the instillation because they may impede the BCG effects, which will interfere with the immunotherapy.

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Conclusion

Defining BCG-refractory disease is a complex undertaking, dependent upon both the timing of therapy as well as the patient response, both symptomatically as well as pathologically. There remains controversy regarding the optimal surveillance strategies involving the recommendations for cystoscopy as well as urinary biomarkers. Similarly, the volume of level 1 evidence available that strongly supports a comprehensive recommendation for maintenance therapies for both nonmuscle invasive bladder cancer and CIS is lacking; nonetheless, patients with BCG-refractory CIS (after 2 induction cycles) should be offered radical cystectomy, and when appropriate, intravesical valrubicin, recognizing the need for strict adherence to continued monitoring. Fortunately, there are several promising new intravesical, oral, and intravenous agents in development that may prove beneficial for these patients as well, and thus obviate the need for bladder removal. The ongoing importance of accruing appropriate patients to these clinical trials must continue to be of paramount interest to all urologists.

References