

Pharmacological Treatments for BCG-Refractory Cancer of the Urinary Bladder

Amy Bronstone, PhD, Jeffrey Dunn, PharmD, MBA, Sam Chang, MD, John Knispel, MD, CPE, Michael Cookson, MD, Cheryl S. Hankin, PhD

Treatment options are limited for persons with carcinoma in situ (CIS) of the urinary bladder who do not improve following surgical eradication and intravesical bacillus Calmette-Guérin (BCG) therapy. Radical cystectomy offers the best opportunity for cure, but this procedure may be inappropriate for some patients and unacceptable to others. Valrubicin (Valstar), first approved by the FDA in 1998, received tentative approval by the FDA on June 10, 2008, and is expected to be reintroduced to the market this year. Valrubicin is the only FDA-approved treatment for BCG-refractory persons with CIS for whom cystectomy is unacceptable. In general, valrubicin is well tolerated and is associated with a modest and durable response rate (absence of disease at 3 or 6 months after therapy initiation). Other intravesical therapies under investigation for persons with CIS may increase the range of therapeutic alternatives available to them. (Drug Benefit Trends. 2008;20:265-272)

Key words: Bladder cancer • Carcinoma in situ • Bacillus Calmette-Guérin (BCG) therapy • Valrubicin

Cancer of the cell lining (transitional cell carcinoma, or TCC) of the urinary bladder is the 4th most common cancer among men and the 11th most common cancer among women in the United States, according to the American Cancer Society.¹ An estimated 68,810 new cases of TCC of the bladder are expected to occur in 2008, resulting in 14,100 deaths.¹ Outcomes are determined by several factors, including the stage and grade of the tumor. Carcinoma in situ (CIS) of the urinary bladder, a type of TCC of the bladder, carries a high risk of recurrence and a moderate risk of stage progression and death.

Persons who have CIS of the

bladder in whom standard treatment—transurethral resection of the bladder tumor (TURBT) followed by intravesical therapy with bacillus Calmette-Guérin (BCG) therapy BCG vaccine (TheraCys, TICE BCG)—fails, have few viable treatment options besides radical cystectomy. Although radical cystectomy is an effective surgical treatment, it poses a high risk of morbidity and mortality for persons with CIS, especially those who are older, are in frail health, and/or have significant comorbidities. However, therapeutic options for persons with recurrent CIS are increasing with the return of FDA-approved valrubicin (Valstar) to the market as well as with contin-

uing research on other investigational therapies, including mitomycin (Mutamycin), gemcitabine (Gemzar), docetaxel (Taxotere), and the combination of interferon alpha-2b (Intron A) and BCG.

Staging and Grading of Bladder Cancer

The bladder consists of 4 major layers of tissue: (1) the urothelium or mucosa; (2) the suburothelial layer of loose connective tissue called the lamina propria; (3) the detrusor muscle, which forms the smooth muscle wall of the bladder; and (4) the fibrous adventitia.² The American Joint Committee on Cancer developed the widely used TNM (tumor-node-metastasis) Staging System to describe the depth of penetration of a tumor and the extent to which the cancer has spread to the lymph nodes and other parts of the body.³ The TNM Staging System for bladder cancer is shown in Table 1.

There are 3 stages of non-muscle-invasive bladder cancer: noninvasive papillary tumors confined to the mucosa (Ta), papillary tumors that invade the lamina propria (T1), and noninvasive flat tumors confined to the mucosa (CIS, also known as Tis).⁴ About 75% of all bladder cancers are diagnosed before they invade beyond the mucosa and lamina propria layers into the detrusor muscle, 20% are diagnosed at the muscle-invasive stage, and 5% are metastatic at diagnosis.⁵ Although non-muscle-invasive cancers have been referred to as “superficial” bladder cancers, clinical practice guidelines now recommend the use of the

Dr Bronstone is director of medical writing at BioMedEcon, Moss Beach, Calif; Dr Dunn is formulary and contract manager at SelectHealth, Inc, Salt Lake City; Dr Chang is associate professor of urologic surgery at Vanderbilt University, Nashville, Tenn; Dr Knispel is regional medical director at Humana, Singer Island, Fla; Dr Cookson is professor of urologic surgery at Vanderbilt University; and Dr Hankin is president and chief scientific officer at BioMedEcon.

Table 1. TNM Staging System for Bladder Cancer^a

Stage	Description
Non-muscle-invasive tumors^b	
Ta	Noninvasive papillary tumor
T1	Papillary tumor invades the lamina propria
CIS of the bladder	Noninvasive flat tumor
Muscle-invasive tumors^c	
T2	Tumor invades muscle
T2a	Tumor invades superficial muscle
T2b	Tumor invades deep muscle
T3	Tumor invades perivesical tissue
T3a	Tumor invades perivesical tissue microscopically
T3b	Tumor invades perivesical tissue macroscopically
T4	Tumor invades the prostate, uterus, or vagina, or the pelvic or abdominal wall
T4a	Tumor invades the prostate, uterus, or vagina
T4b	Tumor invades the pelvic or abdominal wall
Metastatic disease^d	
NX	Regional lymph nodes cannot be assessed
NO	No regional lymph node metastases
N1	Metastasis in single lymph node, 2 cm or less in greatest dimension
N2	Metastasis in single lymph node, > 2 cm but not > 5 cm in greatest dimension; or multiple lymph nodes, none > 5 cm in greatest dimension
N3	Metastases in a lymph node, > 5 cm in greatest dimension
MX	Distant metastases cannot be assessed
MO	No distant metastases
M1	Distant metastases

TNM, tumor-node-metastasis; CIS, carcinoma in situ.

^a American Joint Committee on Cancer Staging Manual. 2002.³

^b Approximately 75% of all bladder cancers are diagnosed at this stage.

^c Approximately 20% of all bladder cancers are diagnosed at this stage.

^d Approximately 5% of all bladder cancers are diagnosed at this stage.

former term.⁶

Stage Ta disease, the most common type of non-muscle-invasive bladder cancer, accounts for about 60% of cases, while T1 and CIS account for about 30% and 10% of cases, respectively.⁷ CIS presents as isolated lesions (primary CIS) in 20% to 30% of cases but more often presents concurrently or consecutively with Ta and/or T1 papillary tumors (secondary CIS).⁸

Tumor grade (low, medium, high) describes the microscopic appearance of bladder cancer cells according to degree of differentiation from normal bladder cells (Table 2).

Risk of Progression, Recurrence, and Mortality in Non-Muscle-Invasive Cancer

Within 15 years of developing non-muscle-invasive bladder cancer, most patients (88%) who survive will experience disease recurrence.⁹ Disease progression is more significant than disease recurrence. Whereas non-muscle-invasive bladder cancers are associated with a lower risk of mortality than muscle-invasive or metastatic tumors, the risk of progression to invasive disease and mortality varies widely among persons with these types of tumors.¹⁰ The stage and grade of bladder cancer indicate its degree of aggressiveness and are prognostic factors (Table 3).⁴ Only 1% to 3% of Ta tumors are high-grade¹¹ compared with 6% to 23% of T1 tumors;¹¹ by definition, all CIS of the urinary bladder are high-grade tumors.¹²

In a combined analysis of 6 Phase 3 trials involving 2535 persons who received treatment for Ta or T1 bladder cancer, the overall progression rate was 9% for participants who received no treatment beyond TURBT.¹³ However, the risk of disease progression was higher in participants with T1 tumors: 30% of participants with T1 tumors experi-

enced disease progression 3 years after TURBT compared with only 4% of participants with Ta tumors ($P < .001$).¹⁴ In contrast, the average disease-progression rate was 54% across 14 clinical trials assessing outcomes for persons who received TURBT for CIS.¹⁵

In a recent multivariate analysis, several prognostic factors were associated with the increased risk of recurrence, progression, and disease-specific mortality in persons with stage Ta or T1 non-muscle-invasive bladder cancer, including the number of tumors, tumor size, tumor grade, and the presence of CIS (Table 4).¹⁶ In another study, the risk of progression increased from 10% to 65% with the presence of CIS.¹⁷ In general, primary CIS is associated with a better prognosis than secondary CIS, which has a risk of invasion of up to 83%.^{18,19}

Standard Treatment for CIS of the Urinary Bladder

Clinical practice guidelines for the treatment of non-muscle-invasive bladder cancer, including CIS of the

Table 2. Bladder Cancer Grading

Tumor Grade	Description
G1 (low)	The cells look like normal bladder tissue cells (well differentiated).
G2 (medium)	The cells look somewhat different (moderately differentiated) from normal bladder tissue cells.
G3 (high)	The cells look unlike normal bladder tissue cells (poorly differentiated).

urinary bladder, were issued by the American Urological Association (AUA) in 1999²⁰ and the National Comprehensive Cancer Network (NCCN) in 2007.⁶ In 2006, the European Association of Urology published guidelines on treating persons with stage Ta and stage T1 non-muscle-invasive bladder cancer²¹ and those with muscle-invasive and metastatic bladder cancer; a separate guideline for treating persons with CIS of the urinary bladder is planned.²²

Both the AUA and the NCCN guidelines indicate that the primary

treatment for persons with non-muscle-invasive bladder cancer is TURBT, an endoscopic surgical procedure in which visible tumors are removed from the bladder by cutting, burning, or using a high-frequency electrical current,^{6,20} unless the patient is too ill or it is not feasible to surgically remove the tumor(s).²⁰ The use of adjuvant intravesical BCG therapy following TURBT for treating persons with CIS of the urinary bladder began in 1976,²³ and BCG therapy was approved by the FDA for treating persons with CIS of the urinary bladder

Table 3. Characteristics of Non-Muscle-Invasive Bladder Cancer

Stage	Description	Non-Muscle-Invasive Tumors, % ^a	Tumors Characterized as High-Grade, %	Likelihood of Recurrence, % ^b	Likelihood of Invasion Into Muscle Following TURBT, %
Ta	Noninvasive papillary tumor	60	1 - 3 ^c	50 - 60	2 - 4 ^d
T1	Papillary tumor invades lamina propria	30	6 - 23 ^c	50 - 70	30 - 50
CIS	Noninvasive flat tumor	10	100 ^e	60 - 90	54 ^f

TURBT, transurethral resection of the bladder tumor; CIS, carcinoma in situ.

^a Dalbagni G. *Nat Clin Pract Urol*. 2007.⁷

^b National Comprehensive Cancer Network. *NCCN Practice Guidelines in Oncology*. Ver 1. 2007.⁶

^c Birch BR et al. *Br J Urol*. 1989.¹¹

^d Heney NM et al. *J Urol*. 1983.¹⁴

^e Pasin E et al. *Rev Urol*. 2008.¹²

^f Lamm DL. *Urol Clin North Am*. 1992.¹⁵

Table 4. Prognostic Factors Associated With Increased Risk of Recurrence, Progression, and Disease-Specific Mortality^a**Risk of recurrence**

Multiple vs single presenting tumors 2.0 times (OR 2.0; 95% CI, 1.60 - 2.4)

Tumor > 3 cm vs tumor < 3 cm 1.7 times (OR 1.7; 95% CI, 1.3 - 2.0)

Presence of CIS 1.6 times (OR 1.6; 95% CI, 1.2 - 2.2)

Risk of progression

Multiple vs single presenting tumors 1.9 times (OR 1.9; 95% CI, 1.1 - 3.2)

G2 vs G1 3.0 times (OR 3.0; 95% CI, 0.4 - 22.8)

G3 vs G1 19.9 times (OR 19.9; 95% CI, 2.6 - 150.0)

Tumor > 3 cm vs tumor < 3 cm 1.7 times (OR 1.7; 95% CI, 1.0 - 3.0)

Presence of CIS 2.1 times (OR 2.1; 95% CI, 1.1 - 4.0)

Risk of disease-specific mortality

G2 vs G1 1.7 times (OR 1.7; 95% CI, 0.2 - 13.9)

G3 vs G1 14.0 times (OR 14.0; 95% CI, 1.8 - 109.0)

Presence of CIS 3.0 times (OR 3.0; 95% CI, 1.4 - 6.6)

OR, odds ratio; CI, confidence interval; CIS, carcinoma in situ; G, grade.

^a Millán-Rodríguez F et al. *J Urol*. 2000.¹⁶

in 1990.²⁴ The precise mechanism of action of BCG therapy in the management of CIS of the urinary bladder is unclear, but the vaccine appears to produce a T-cell-mediated immune response that may increase antitumor activity.²⁵

As an intravesical therapy, the instillation of BCG is administered into a patient's bladder via a catheter, retained for approximately 2 hours, then eliminated.²⁵ The usual course of BCG therapy is 6 weekly intravesical instillations followed by 4 to 6 weeks of rest with a reevaluation 12 weeks after therapy initiation.⁶ Persons with CIS of the urinary bladder who have recurrent or persistent disease at week 12 may be given a second course of BCG therapy and reevaluation after 3 months.⁶ For persons who respond to BCG therapy after 1 or 2 courses of treatment, maintenance BCG therapy may re-

duce disease recurrence and progression²⁶; however, the ability of BCG therapy to improve long-term survival is controversial.^{27,28}

BCG therapy following TURBT for persons with CIS of the bladder improved the response rate from 51.5% (using adjuvant chemotherapy) to 68.1%.²⁹ A review of 34 clinical trials of adjuvant BCG therapy for persons with CIS showed an average complete response rate of 72%.³⁰

Although introduction of BCG therapy has improved outcomes for many persons with CIS of the bladder, a substantial number do not experience initial or sustained benefit from this standard treatment. Some patients may need to discontinue BCG therapy prematurely because of their inability to tolerate adverse effects (urinary frequency and burning, mild malaise, low-grade fever, septic and/or hypersensitivity reac-

tion),⁵ which are more severe and more frequent than the adverse effects of intravesical chemotherapy.³¹ In a study of 487 persons with stage Ta or stage T1 non-muscle-invasive bladder cancer who had expected to receive BCG therapy for 36 months, 20.3% discontinued treatment prematurely because of adverse effects.³²

Patients who can tolerate BCG therapy may not respond to it, while other patients may have a recurrence after they initially respond to treatment. Such patients are often referred to as "BCG failures" or BCG-refractory patients. Despite the high initial rate of response to BCG therapy (about 70%), on average, 34% of patients eventually experience disease recurrence, and only 46.7% of patients are disease-free at a median follow-up of 3.6 years.²⁹ The 5-year disease-free rate associated with

BCG therapy is 45%,³³ and the 10-year disease-free rate is 30%.^{34,35}

Maintenance BCG therapy may improve the response rate in persons with CIS of the bladder. Although several early studies did not show a significant benefit of BCG maintenance therapy,^{36,37} a large, randomized, controlled study found that only 142 of 278 persons (51%) with CIS who received an initial course of BCG therapy were disease-free at 3 months after therapy initiation, and a 3-week course of maintenance BCG therapy given at 3, 6, 12, 18, 24, 30, and 36 months after the initial course of BCG therapy increased the response rate in persons with CIS to 68%, which was significantly higher than for persons not receiving maintenance BCG therapy ($P = .004$).²⁶

Alternative Treatment Options

Radical cystectomy. Persons who are intolerant of BCG therapy or are BCG-refractory have limited treatment choices. The therapeutic option with the highest cure rate is radical cystectomy, which has an average recurrence-free survival rate of 89% and 85% at 5 and 10 years, respectively, in patients with non-muscle-invasive cancer (excluding T1 disease) without lymph-node involvement.³⁸ However, not all patients with CIS of the bladder may benefit from radical cystectomy, which can be associated with unacceptable morbidity and mortality for older and/or frail patients with comorbid diseases. Early complications are experienced by 28% of patients after radical cystectomy, and there is a 2.5% perioperative mortality rate.³⁸ Patients with a higher burden of comorbid disease have significantly lower rates of disease-specific survival ($P = .049$) and overall survival ($P = .016$) following radical cystectomy.³⁹ In a study of 888 persons who underwent radical cystectomy for TCC of the urinary bladder, ad-

vanced age was associated with a higher risk of disease-specific mortality (hazard ratio 1.017; 95% confidence interval, 1.004 to 1.031; $P = .013$), even after controlling for staging and grading of bladder cancer.⁴⁰

Consequences and distressful symptoms. Some patients who are healthy enough to undergo radical cystectomy may wish to avoid the lifestyle-altering consequences. For example, patients who are not candidates for continent cutaneous diversion or orthotopic urinary diversion may need to be fitted with an external appliance to collect urine from the stoma.⁴¹

Distressful symptoms of cystectomy may include increased GI, bowel, and sexual dysfunction. A population-based study of 251 persons (201 men, 50 women) and 310 controls showed that after radical cystectomy, participants reported a 3-fold increase in bowel symptom distress, and were more likely to experience defecation urgency (a 5-fold [reservoir] increase and a 9-fold [conduit] increase), fecal leakage (a 4-fold [reservoir] increase and a 6-fold [conduit] increase), abdominal pain, and diarrhea than the control group.⁴² Surgery was associated with a 6-fold (conduit) to 7-fold (reservoir) increase in the incidence of urinary tract infections with fever as well as a 4-fold (reservoir) and to 7-fold (conduit) increase in urine odor intensity.⁴² Women who underwent radical cystectomy experienced a 4-fold (reservoir) and 6-fold (conduit) reduction in perceived physical attractiveness compared with the control group, while men who underwent surgery reported an 11-fold (reservoir) and 13-fold (conduit) decrease in perceived physical attractiveness.⁴² All men who underwent cystectomy lost the ability to ejaculate and were 2 times as likely to experience erectile dysfunction.⁴²

Because of these well-known limitations, physicians may hesitate

to recommend this as a treatment option until patients do not improve after receiving multiple conservative treatments. Only 5% of US urologists responding to a survey indicated that they would recommend cystectomy for persons with CIS of the bladder for whom a single induction course of BCG therapy failed; 40% of respondents said they would recommend cystectomy in persons with CIS of the bladder in whom 2 courses of BCG therapy had failed.⁴³

Pharmacological treatment options. NCCN treatment guidelines note that pharmacological treatments are available for persons with CIS of the urinary bladder who are intolerant to BCG therapy or are BCG-refractory and who may desire an alternative to radical cystectomy. These treatment options are FDA-approved intravesical valrubicin and several investigational intravesical treatments, including mitomycin, interferon alpha-2b, and interferon alpha-2b plus BCG.⁶

Valrubicin. In 1998, valrubicin, a semisynthetic, lipid-soluble analog of the anthracycline doxorubicin, became the first drug approved by the FDA for treating persons with CIS of the urinary bladder who are BCG-refractory.⁴⁴ Valrubicin, which is expected to be reintroduced to the US market in 2008, remains the only FDA-approved treatment for BCG-refractory patients with CIS of the bladder for whom cystectomy is unacceptable because of the rigors of the surgery and the high risk of morbidity and mortality.⁴⁴ (Valrubicin had been removed from the market in 2002 when its manufacturer, Anthra Pharmaceuticals, detected some degradation problems [not efficacy of safety problems] with the formulation. Valrubicin was then placed on the FDA Drug Shortages List. In April 2006, Valera Pharmaceuticals acquired rights to valrubicin for this indication. Indevus Pharmaceuticals

secured the rights with its acquisition of Valera in 2007.)

The efficacy and safety of valrubicin have been demonstrated in patients who received extensive treatment for recurrent CIS of the urinary bladder. In a phase 2 study, 90 patients who had been given at least 2 courses of intravesical treatment, including at least 1 course of BCG therapy (70% of patients had received at least 2 courses of BCG therapy), received TURBT followed by 6 weekly doses of 800 mg of intravesical valrubicin therapy.⁴⁵ Six months after therapy initiation, 19 patients (21%) who received valrubicin were disease-free and had a median time to failure (defined as pathological evidence of bladder cancer or positive cytology results on 2 consecutive evaluations with a missing or negative biopsy result) of 18 months or longer. In addition, 10 patients (11.1%) with recurrent CIS of the urinary bladder who had incomplete responses experienced regression of CIS of the bladder to low-grade papillary tumors. Thus, 29 of 90 patients (32%) experienced clinical benefit from valrubicin. The treatment was well-tolerated; most adverse events were local bladder symptoms, which were mild to moderate in severity, self-limited, and easily managed. Study data demonstrated that valrubicin is an effective and relatively safe agent for BCG-refractory persons with CIS of the bladder, with approximately 1 in 5 patients having a durable response to treatment.

Persons with CIS of the bladder who delayed cystectomy for 3 months while receiving valrubicin did not appear to be at undue risk of mortality. The low risk of mortality associated with delaying cystectomy, at least for a brief period, was confirmed by Cheng and colleagues,⁴⁶ who found that after controlling for patient age, there was no difference in survival between persons with

CIS of the bladder who underwent immediate cystectomy (within 3 months of diagnosis) and those who delayed cystectomy ($P = .16$). In contrast, other researchers found that persons with refractory non-muscle-invasive disease who delay cystectomy for more than 2 years have a significantly reduced 15-year disease-specific survival rate compared with patients who delay surgery for less than 2 years (26% vs 69%, $P = .003$).⁴⁷

Investigational pharmacological treatments. The only data supporting the use of mitomycin come from a single small ($N = 21$) study of BCG-refractory persons with CIS of the urinary bladder.⁴⁸ Although the study yielded a response rate similar to that of valrubicin, no information was provided about the durability of response, and no additional studies have confirmed these results.

Interferon alpha-2b monotherapy does not appear to be particularly efficacious for treating BCG-refractory persons with CIS of the bladder. In an analysis of persons with CIS of the bladder and/or papillary TCC who were BCG-refractory and who received interferon alpha-2b therapy, the durable response rate was only 12%.⁴⁹

A phase 2 study of 467 patients for whom BCG therapy failed (27% of whom had CIS of the bladder) demonstrated a disease-free rate of 45% at a median follow-up of 2 years among all patients who received combination interferon alpha-2b and BCG therapy after 1 course of BCG monotherapy.⁵⁰ Patients who had had 2 or more courses of BCG therapy had significantly poorer outcomes than those who had 1 or no previous courses of therapy (HR 1.56; $P = .0002$).⁵⁰

Although the final study report did not reveal the response rate among patients with CIS of the bladder, a preliminary report of the findings showed that patients with per-

sistent CIS after a single course of BCG therapy ($N = 22$) had a much lower response rate after treatment with interferon alpha-2b and BCG, with only 23% of patients disease-free at 24 months.⁵¹

Other therapeutic options under investigation for persons with non-muscle-invasive bladder cancer (including CIS of the urinary bladder) who are refractory to BCG therapy or other intravesical therapies include intravesical gemcitabine^{52,53} and intravesical docetaxel.^{54,55}

Conclusion

Persons with CIS of the urinary bladder who experience disease recurrence following BCG therapy have few other treatment options. Although radical cystectomy offers the highest rate of survival in BCG-refractory patients, the surgery also presents a substantial risk of morbidity and mortality. Consequently, physicians may be reluctant to recommend radical cystectomy for patients who are older, are frail, and/or have significant comorbidities. Patients who are well enough to withstand the rigors of surgery may choose nonsurgical treatment in lieu of surgery or as an interim alternative. For such patients, a 6-week course of valrubicin is the only FDA-approved treatment for BCG-refractory patients with CIS of the urinary bladder for whom cystectomy is unacceptable. Valrubicin, which previously appeared on the FDA Drug Shortages List, is expected to be reintroduced to the market later this year. Other investigational pharmacological treatments for BCG-refractory patients with CIS of the bladder are in phase 2 trials. Given the paucity of nonsurgical options for such patients, the reintroduction of valrubicin and the emergence of new alternatives are welcomed. ■

continued

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