

INTRAVESICAL THERAPY AND FOLLOW-UP OF SUPERFICIAL TRANSITIONAL CELL CARCINOMA OF THE BLADDER

ESCHELLE STAPP, ARLINE D. DEITCH, RALPH W. DEVERE WHITE

Department of Urology, University of California Davis School of Medicine, Sacramento, California, USA

ABSTRACT

Intravesical therapy is commonly used for the treatment of superficial transitional cell carcinoma (TCC) of the bladder. There are 2 major categories of intravesical therapy; chemotherapy and immunotherapy. The 2 types have different indications and different mechanisms of action.

Chemotherapy: there is evidence that intravesical therapy fails to affect disease progression, nevertheless, chemotherapy in the form of thiotepa, mitomycin-C, doxorubicin or epirubicin has been recommended for those patients having low-grade, low-stage tumors (Ta, Grade 1-2) who have multiple tumors at presentation or whose recurrence rate on follow-up is unacceptable. While intravesical chemotherapy reduces the risk of recurrence during the first 3-6 month period after TUR, the difference in recurrence rates becomes less significant with increasing time after resection.

Immunotherapy: unlike chemotherapy, intravesical immunotherapy in the form of BCG has been shown to reduce tumor recurrence and prevent progression. Patients who are suitable candidates for intravesical BCG include those with carcinoma in situ (CIS), or with T1 lesions that have been completely or incompletely resected, as well as those patients who have failed intravesical chemotherapy for low-grade, low-stage tumors. BCG must never be given immediately after tumor resection due to the possibility of severe systemic infection.

To summarize, the authors practice regarding intravesical therapy for superficial bladder cancer, is the following: 1)- for patients at low risk of progression, we initially resect the tumor and do not treat with intravesical therapy; 2)- for patients at low risk of progression but with high risk of recurrence, (e.g., those with high grade TCC that are either stage Ta or stage T1), we treat with an immediate single post-TUR dose of thiotepa of 30 mg; 3)- for recurrent, low risk tumors, we treat with a course of thiotepa; 4)- for patients with a high risk for progression (e.g., those with high grade TCC and stage T1), we administer a 6-week course of BCG; 5)- for patients at high risk for progression, where the next tumor recurrence would indicate a cystectomy, we will treat with a 6-week course of BCG followed by maintenance.

Key words: bladder, transitional cell carcinoma, chemotherapy, immunotherapy

Braz J Urol, 26: 242-249, 2000

INTRODUCTION

Intravesical therapy is commonly used for the treatment of superficial transitional cell carcinoma (TCC) of the bladder. However, there is considerable debate as to when to implement this therapy and which type of intravesical treatment is most appropriate. Moreover, even if the decision is made to adopt intravesical therapy, questions remain as to whether maintenance therapy should be undertaken and how

often and when to follow these patients. These treatment decisions affect a substantial number of patients since more than 50,000 cases of transitional cell carcinoma of the bladder are diagnosed annually in the United States alone (1).

TCC is the most common histological type of bladder cancer seen throughout the world. In the United States, if one includes both the initial presentation and recurrences, 92% of cases are superficial TCC which are designated as either stage Ta or T1

SUPERFICIAL CARCINOMA OF THE BLADDER

Table 1 - Impact of tumor stage and grade on disease progression in patients with superficial TCC

Study	Patients	Follow-up	Rate of Progression
National Bladder Cancer Group Heney NM	207	Median 39 months	Grade 1 : 2% Grade 2 : 11% Grade 3 : 45% Stage Ta : 4% Stage T1 : 30%
Holmang et al.	176 (65 had definitive treatment)	At least 20 years or death	Stage Ta : 14% Stage T1 : 39%
EORTC-GU Group Kurth et al.	423 treated with TUR alone or TUR plus doxorubicin or ethoglucid	Median 10.7 years	Stage Ta : 9% Stage T1 : 22%

(Ta: confined to the epithelium; T1: penetrating the lamina propria but not into muscle). The primary treatment for Ta/T1 TCC is transurethral resection (TUR). In a compilation of data from 3,404 patients in 21 trials comparing TUR alone versus TUR plus intravesical chemotherapy, Lamm showed that only 49% of patients remained recurrence-free after TUR alone (2). That review advocates the use of intravesical therapy solely for those patients who are at high risk of tumor recurrence or disease progression. Even when all visible tumor is completely resected by TUR, the overall risk of recurrence remains approximately fifty percent. Recurrence is not in itself life threatening, unless the recurring tumors progress to a higher stage. There have been a number of studies showing that the progression rate for Ta lesions is very different from that for T1 lesions. For stage Ta disease, the progression rate is approximately 5-9%, while it is as high as 45% for stage T1 TCC. Moreover, the grade of the tumor

also plays an important role in disease progression. While Ta lesions tend to be grade 1 or 2 and are rarely grade 3, T1 lesions can often be grade 3, putting these tumors in a much higher risk category (Table-1).

Thus, intravesical therapy is appropriately administered to those patients who are found to be at higher risk of recurrence after the initial TUR, based on their tumor characteristics (Table-2). When treating patients who have high-risk lesions, the clinical aim is to avoid the need for cystectomy and to decrease the potential chance of death from TCC. However, if intravesical therapy is employed for those having low risk lesions, the clinical goals are different. For the latter patients, the goal is to try to increase patient comfort and reduce health care costs by decreasing the need to intervene for recurrences.

There are 2 major categories of intravesical therapy, chemotherapy and immunotherapy. The 2 types have different indications and different mechanisms of action. In addition, there is some controversy

Table 2 - Superficial bladder cancer tumor characteristics

Low Risk or "Favorable"	Higher Risk or "Unfavorable"
Single tumor	Multiple tumors
Stage Ta	Stage T1
Low grade	High grade
No CIS*	CIS or cytological atypia or dysplasia
Diploid	Aneuploid
Negative cytology	Positive cytology

* Carcinoma-in-situ defined as a high-grade intraepithelial lesion

regarding the timing of administration of intravesical chemotherapy, i.e., is immediate adjuvant chemotherapy reasonable? We will explore these and other issues regarding intravesical therapy and will highlight key points about following patients with superficial bladder cancer.

INTRAVESICAL CHEMOTHERAPY

In general, after a bladder tumor has been resected and a bimanual examination has been performed, the histological characteristics of the tumor will dictate whether or not to use intravesical therapy. As discussed above, if a tumor belongs to the high-risk group, then intravesical treatment is reasonable to use in order to prevent cancer recurrences and, if possible, to halt progression to muscle-invasive disease. The former goal is often achieved, while the latter is more doubtful.

Why do superficial bladder tumors recur? In a recent review by Akaza et al., this question is addressed and possible explanations are given (3). These authors surmise that there are four reasons for recurrence that are not mutually exclusive: 1)- implantation ("seeding" or dispersion) of tumor cells in the epithelium during tumor resection, 2)- growth of co-existing microscopic lesions, 3)- an incomplete TUR resulting in tumor cells being left behind, and 4)- the emergence of a "second primary" or of new bladder tumors. It is the total of all these types of "recurrences" that we try to prevent by using intravesical therapy. Specifically, the use of intravesical chemotherapy has been shown to decrease the recurrence rate of low-grade, low-stage tumors. Some of the most compelling data on this subject comes from the Fourth International Consensus Conference on Bladder Cancer in 1993. This conference concluded that, compared to no adjuvant therapy, intravesical chemotherapy provided a 12-15% lower tumor recurrence rate. It is noteworthy that this conference also concluded that intravesical chemotherapy had no effect on progression to higher disease stages. Both of these observations are supported by the work of Lamm (2), who examined the long-term results of 1,938 bladder cancer patients treated with intravesical chemotherapy and compared them to

2,607 who did not receive adjuvant therapy. No significant survival or progression advantages were demonstrated for those receiving adjuvant intravesical therapy. Akaza et al. have offered a hypothesis explaining why reducing tumor recurrences does not influence disease progression (3). This group proposes that intravesical therapy has no effect on the subsequent emergence of second primary tumors, which may then be responsible for progression. However, they considered that intravesical therapy is effective against dispersion of the original tumor during TUR as well as against residual microscopic foci or otherwise incomplete resections. This theory seems plausible, and underscores the need for prevention of disease progression, which can ultimately lead to death.

Despite the above evidence that intravesical therapy fails to affect disease progression, chemotherapy in the form of thiotepa, mitomycin-C, doxorubicin or epirubicin has been recommended for those patients having low-grade, low-stage tumors (Ta, Grade 1-2) who have multiple tumors at presentation or whose recurrence rate on follow-up is unacceptable. Akaza et al. contention that intravesical therapy is not effective against the "second primary" tumor (3) is based on their data plotting the frequency of tumor recurrence at given timepoints after TUR. While intravesical chemotherapy reduces the risk of recurrence during the first 3-6 month period after TUR, the difference in recurrence rates becomes less significant with increasing time after resection. Their explanation for these observations is that recurrences due to implanted cells and microscopic tumor lesions are affected by the intravesical chemotherapy, but that the risk of "recurrence" due to the appearance of new primary tumors is not affected. Such tumors will become manifest considerably later after resection. While this explanation might lead one to question the value of using any intravesical chemotherapy, we believe that chemotherapy does have a role to play in the treatment of superficial bladder cancer. There is an obvious benefit to the patient if this therapy can reduce the number of recurrences or, at the least, lengthen the time between recurrences. However, it has become evident that maintenance therapy is needed to achieve

the full beneficial effects of intravesical chemotherapy. The National Bladder Cancer Cooperative Group (NBCCG) conducted a prospective randomized trial in which treatment with thiotepa delayed time to recurrence in most patients until after they had stopped a two-year course of monthly maintenance therapy.

In addition to the standard administration of intravesical chemotherapy (i.e., starting after a period of 1-2 weeks post-resection), there has been recent interest in using immediate post-surgery adjuvant intravesical chemotherapy. In a recent review by Schellhammer, the data resulting from this latter form of treatment is clearly outlined (4). The rationale for immediate post-resection adjuvant intravesical chemotherapy is based on the first mechanism of tumor recurrence cited above, namely the implantation or "seeding" of tumor at the time of resection. The concept is that a denuded epithelial bed exists secondary to transurethral resection. This, coupled with the concomitant release of tumor cells, may provide the fertile "soil and seed" for tumor regrowth. One of the most significant of the initial small trials of this early adjuvant chemotherapy was a prospective, randomized trial by Zincke et al. which compared immediate adjuvant treatment with thiotepa (60 mg) or doxorubicin (50 mg) versus saline (control). This study reported recurrences in only 30% of the group treated by intravesical thiotepa, 32% in those receiving doxorubicin, compared to 71% in the control group (4). Should we therefore conclude that the 40% reduction in recurrences resulted from prevention of tumor cell seeding? On the face of it, this appears to be highly unlikely. Furthermore, it seems improbable that a single dose of thiotepa could cure microscopic or residual disease. Part of the problem in interpreting these data is that the 71% recurrence rate in the control group is 20% higher than that reported by others. Nevertheless, whatever the reasons for these findings, other clinical trials have reported similar results. For example, the European Organization for Research on Treatment for Cancer (EORTC) conducted a study of 431 patients comparing a single dose of epirubicin (80 mg) to controls receiving intravesical water. This study demonstrated a clear advantage of immediate

epirubicin therapy in reducing tumor recurrence. Schellhammer's paper (4) also raises the concept of combining immediate intravesical chemotherapy with a subsequent Bacillus Calmette-Guerin (BCG) induction course initiated 1-2 weeks later with subsequent maintenance of BCG treatment. We believe that such a combined chemo and immunotherapy approach may very well reduce both recurrence and progression. It is important to stress that BCG cannot be used immediately after resection due the potential for systemic absorption. If we are going to use a course of intravesical immunotherapy, we see no advantage to administering immediate chemotherapy.

For the patient with low risk of progression, we recommend instilling a single dose of thiotepa after resection as this will save the patient coming 6 weeks in a row to receive intravesical therapy. If the single dose fails to stop recurrence, it is highly unlikely that at the next visit and at 3 and 6 months post-resection that these patients will experience disease progression.

The available data on intravesical chemotherapy does not indicate that any single agent currently in use is clearly better than any other. Therefore, selection of a chemotherapy agent is usually based on cost, toxicity, and availability as well as on physician preference and experience. There is an advantage to using a limited number of agents so that standard protocols can be adopted, thereby reducing errors in drug administration.

We will consider 4 chemotherapy agents that have been used with some success in the adjuvant treatment of bladder cancer. Thiotepa is an alkylating agent of molecular weight 189.22 that inhibits nucleic acid synthesis. Typically, it is administered in an intravesical dose of 30-60 mg (1mg/ml in sterile saline or water), weekly for 6 weeks, then monthly for up to 1 year. While thiotepa is inexpensive, it can have serious side effects. In approximately 5% of patients, myelosuppression may result due to the low molecular weight of this compound, which permits systemic absorption to occur. Therefore, the white blood cell (WBC) count must be checked prior to giving the next dose. If the WBC counts are down, the dose is withheld. About 25% of the patients receiving

intravesical thiotepa report irritative voiding symptoms. However, this is clearly a lower rate than that found for patients receiving BCG. The efficacy of thiotepa varies in the literature, probably due to the variable doses and regimens that have been employed. Lamm reviewed 10 controlled studies with 1,009 patients treated with thiotepa and found that the recurrence rate was 45% in the thiotepa group as compared to 62% in the control group. However, in 5 out of the 10 series, statistical significance was not reached. Thiotepa is probably best reserved for those having stage Ta lesions. Indeed, this patient group is the one studied in the early thiotepa studies reported by Dr. Koontz.

Mitomycin C (MMC) is an alkylating agent that is cell-cycle nonspecific with a molecular weight of 329. The usual dose is 20-60 mg and side effects are minimal. This drug is not readily absorbed so systemic effects are rare. However, allergic reactions such as a palmar rash occur in approximately 10% of cases. A study conducted by the EORTC examined the use of MMC for existing papillary tumors and found a complete response rate of 43% (270 of 627). When used for carcinoma-in-situ (CIS), 58% of patients had resolution of disease. For prophylactic use, MMC has a relative advantage of 15% over no chemotherapy. The use of maintenance therapy after MMC is controversial but probably is not advantageous (2).

Doxorubicin is a high molecular weight (580) anthracycline antibiotic that acts as an intercalating agent and is most toxic to S-phase cells. It is usually given in a dose of 30-100 mg administered either weekly or every 3 weeks. Chemical cystitis with this agent can be severe, occurring in 25-50% of patients. This side effect is reversible with cessation of drug treatment. The success rate of doxorubicin as first line treatment is approximately 40% overall. It does not appear to have significant advantage over no additional treatment when used prophylactically (2). Maintenance therapy with this drug is without value. For all of the above reasons, we very seldom employ doxorubicin for treatment of TCC. A derivative of doxorubicin, epirubicin, has become increasingly used. It has fewer side effects with similar antitumor effects to doxorubicin. The dose of epirubicin is 30-

80 mg in saline given daily for 3 days with a rest period followed by 3 more daily instillations.

Intravesical chemotherapy clearly reduces short-term recurrence in superficial bladder cancer when compared with no additional treatment. The relative advantages are 17% for thiotepa, 15% for mitomycin-C and 18% for doxorubicin (2). However, long-term reduction in tumor recurrence does not occur and intravesical chemotherapy does nothing to prevent tumor progression. Furthermore, there have been no documented survival advantages for adjuvant intravesical chemotherapy.

INTRAVESICAL IMMUNOTHERAPY

Unlike chemotherapy, intravesical immunotherapy in the form of BCG has been shown to reduce tumor recurrence and prevent progression. We consider it to be the most effective form of intravesical treatment for superficial bladder cancer. While BCG is an immune stimulant or modulator (5), the exact mechanism of action of BCG on TCC is unknown. BCG causes an inflammatory reaction in the bladder leading to production of cytokines (interleukins 1, 2 and 6, interferon gamma and tumor necrosis factor alpha). It is thought that, as a result of BCG treatment, macrophages and lymphocytes infiltrate the bladder and destroy tumor cells. There is some evidence that BCG instillation involves not only local immunological efforts but also systemic immune responses (6). BCG therapy has been shown to be superior to chemotherapy in reducing disease progression. Nseyo & Lamm have tabulated the results of 6 clinical studies comparing surgery alone with intravesical BCG immunotherapy and have shown that 5 out of the 6 studies demonstrate a significant advantage of BCG therapy (5). The 1 study that was not able to show a significant advantage had only 77 patients and had a fairly high recurrence rate for the controls of 42%.

Patients who are suitable candidates for intravesical BCG include those with CIS, or with T1 lesions that have been completely or incompletely resected, as well as those patients who have failed intravesical chemotherapy for low-grade, low-stage tumors (1). As mentioned previously, BCG must never be given immediately after tumor

resection due to the possibility of severe systemic infection.

Optimal BCG therapy depends on the appropriate use and understanding of the basic principals of this immune modulator. BCG must have direct contact with the tumor cells. Furthermore, the tumor burden should be minimized prior to therapy and an adequate number of viable bacteria must be used. Although complete response rates of 60% or more have been reported for BCG treatment of residual Ta or T1 TCC, it is best to resect as much tumor as possible before the onset of treatment (5). Toward this end, the use of vaportrodes to eradicate a large bulk of tumor is beneficial. The best dose of BCG has yet to be defined, however, there are current recommendations for the 2 commercially available preparations (TheraCys-Connaught, and TICE-Organon) (7). The usual doses advocated are 81 mg of TheraCys or 50 mg of TICE BCG in 50 cc normal saline instilled through a catheter. We typically wait 2 weeks after TUR before beginning treatment with BCG. Once the BCG has been instilled, we ask the patients to hold the instilled fluid in their bladders for approximately 2 hours, and have them change positions frequently in order to distribute the medication throughout the bladder. It is important to be sure that the patient can do this. We not infrequently see patients who say they have failed therapy using BCG but, by our standards, we believe that they have never been adequately treated.

To date, there is no completely accepted schedule of administration for BCG. It has, however, been shown that approximately 50% of patients will not be successfully treated by a single 6-week course of BCG. A Southwest Oncology Group (SWOG) study compared 2 treatment arms. Arm 1 consisted of an induction course of 6 weekly treatments with BCG. Arm 2 consisted of the same induction course followed by 3 months off-therapy, and a subsequent maintenance protocol in which BCG was administered once weekly for 3 weeks. This maintenance protocol was repeated every 6 months for 3 years. Comparing the 2 treatment arms, complete response was increased from 68% to 84% when a single maintenance regimen was utilized (5). Long-term disease-free status and, most important, patient survival were increased as well when the 3

weekly maintenance courses were employed (1). The largest response rate differences was apparent at month 3, at the time when the first maintenance treatment was administered.

The toxicity of this treatment must be considered when deciding on the best BCG schedule. In the SWOG study cited above, significant toxicity requiring cessation of therapy, decreased dose or administration of isoniazid (INH) therapy, occurred for 26% of patients receiving maintenance therapy as compared to only 9% of those receiving BCG induction alone ($p < 0.0001$).

Taking the above information into consideration, it appears that some patients will benefit from maintenance BCG therapy. However, for patients who are receiving BCG due to "failed" intravesical chemotherapy for low-grade tumors, the increased risk of toxicity encountered using maintenance therapy may not be justified. In this population, it seems reasonable to use either a 6-week induction courses or a 6-week induction followed by a 3-weekly course at 3 months. However, if a patient has CIS and/or a T1 grade 3 tumor, maintenance should be attempted. This is especially true if the patient has tolerated the induction course without significant toxicity. Recently, the question of whether or not to biopsy at the 3-month period after the initial BCG treatment has been examined in detail. Routine biopsy was part of the SWOG study cited above and tends to be carried out in general practice. However, this procedure is uncomfortable for the patient and is very expensive. Dalbagni et al., from Memorial Sloan-Kettering reviewed 81 of their patients who had undergone routine biopsy at 3 months after BCG treatment (8). They found that 58% of these patients had a complete response (negative biopsy) at 3 months and that a negative cystoscopy correlated well with a negative biopsy. However, only 10% of patients who had erythematous lesions had a positive biopsy. Therefore, the authors advocate evaluating the need for biopsy combining the cystoscopic appearance of the bladder and the results from cytological examination. If the patient has a normal-appearing bladder or has erythema with a negative urine cytology, biopsy is deferred at the 3-month period. However, this group still biopsies all patients at 6 months. The question can thus be raised

about the usefulness of the biopsy at 6 months. It is necessary? Can one avoid biopsies altogether? At present no data exists to support not biopsying these patients. It is to be hoped that such data will be available soon to help us to identify those who can avoid a routine biopsy as part of follow-up.

Our current protocol for BCG treatment is as follows: For patients who do not have CIS and who do not have recurrent tumors at the first cystoscopy 3 month following resection, we do not perform biopsies and we follow these patients with standard 3-monthly cystoscopies. If however, the initial lesion was especially aggressive-appearing (Stage T1, Grade 3 multifocal lesions with or without CIS), or if there is concomitant CIS, we will obtain a biopsy. If that is negative, we wait 2 weeks and give a 3-week course of BCG. If the resected tumor was less aggressive, we administer a 3-weekly course of BCG that is initiated at the first 3-month cystoscopy following resection, providing that this first cystoscopy is clear of tumor. We then repeat cystoscopy at 6 months. If this is clear, we do not give BCG at this time, but wait for the 9-month cystoscopy and then repeat the 3-weekly course of BCG (Table-3).

We are presently reviewing all of our cases to try and develop reliable data to allow us to reduce the number of biopsies.

Treatment with BCG, one of the most effective agents against superficial bladder cancer, can result in a wide range of side effects, and the toxicity of this drug must be recognized. Some of the symptoms associated with the use of BCG are relatively minor and common, whereas others are more serious and must be treated promptly. For example, cystitis is the most frequent side effect of BCG therapy, and may be seen in up to 90% of patients. Dysuria and urinary frequency are also expected symptoms due to the inflammatory

response to BCG therapy, but these symptoms are usually not present until the 3rd or 4th treatment. Most often, these latter symptoms will resolve within 24 hours and acetaminophen, pyridium and/or anticholinergic medication may be of some help. However, severe irritative voiding symptoms, or those lasting more than 72 hours can be treated with 300 mg per day of isoniazid (INH). This treatment can be continued for 1-2 weeks or until the symptoms have been resolved (7). It is however unnecessary to administer continuous treatment with INH. Some physicians advocate giving 300 mg INH one day prior to subsequent BCG instillations and continuing for 3 days after treatment with BCG (5). BCG treatment should not be repeated until all side effects from the previous treatments have resolved. This is especially true of hematuria, which can occur in approximately 20-35% of patients.

Other, non-life-threatening symptoms, which may occur in about 20% of patients, include malaise, fatigue, and lethargy. A low-grade fever of less than 101 degrees Fahrenheit can also be seen in approximately 10-15% of patients, but this usually is resolved within 24 hours. It is important to distinguish these less severe and short-lived side effects from the more serious symptoms of systemic infection.

Any patient who develops a fever of greater than 103 degrees Fahrenheit should be hospitalized and treated for BCG sepsis. Other symptoms include shaking chills and hypotension. Sepsis, although rare, can be fatal if not treated quickly. The current recommendations for treatment are INH 300 mg, rifampin 600 mg, and prednisone 40 mg, daily. Blood cultures need to be obtained and broad-spectrum antibiotics should be administered until the culture results are returned. Frequently, however, with BCG sepsis, blood cultures can be negative. Treatment with

Table 3 - Schedule for BCG treatment

Time period after initial tumor resection	Cystoscopy	BCG treatment
2 weeks	No	6-week induction
3 months	Yes, +/- biopsy	3-weekly maintenance
6 months	Yes	No
9 months	Yes	3-weekly maintenance

prednisone should be given until sepsis resolves and then the dose should be tapered for 1-2 weeks. The INH and rifampin are generally continued for 3-6 months. Patients who have experienced BCG sepsis should not receive BCG again.

INTERFERON

We will not discuss treatment with interferon due to its expense. Because of the relative ineffectiveness of this agent, we no longer employ it in the treatment of TCC.

CONCLUSIONS

To summarize our practice regarding intravesical therapy for superficial bladder cancer, we would like to stress the following points:

For patients at low risk of progression, we initially resect the tumor and do not treat with intravesical therapy.

For patients at low risk of progression but with high risk of recurrence, (e.g., those with high grade TCC that are either stage Ta or stage T1), we treat with an immediate single post-TUR dose of thiotepa of 30 mg (off protocol).

For recurrent, low risk tumors, we treat with a course of thiotepa.

For patients with a high risk for progression (e.g., those with high grade TCC and stage T1), we administer a 6-week course of BCG.

For patients at high risk for progression, where the next tumor recurrence would indicate a cystectomy, we will treat with a 6-week course of BCG followed by maintenance.

It is to be hoped that in the future molecular markers will better define the risk groups for

recurrence and progression of TCC. Ideally, such markers will also serve to define the appropriate choice of intravesical therapy for this disease.

REFERENCES

1. de Vere White RW, Carroll P, Grossman HB, Sarosdy M: Contemporary management of bladder carcinoma. Course at American Urological Association National Meeting, Dallas Tx, 1999.
2. Lamm DL: Long-term results of intravesical therapy for superficial bladder cancer. *Urol Clin North Am*, 19: 573-580, 1992.
3. Akaza H, Kurth KH, Williams R, Hinotusu S: Intravesical chemotherapy and immunotherapy for superficial tumors: Basic mechanism of action and future direction. *Urol Oncol*, 4: 121-129, 1998.
4. Schellhammer PF: What is the available evidence to support immediate adjuvant intravesical chemotherapy after transurethral resection of superficial transitional cell carcinoma of the bladder? *Urol Oncol*, 4: 73-79, 1998.
5. Nseyo UO, Lamm DL: Immunotherapy of bladder cancer. *Sem Urol Oncol*, 13: 342-349, 1997.
6. Taniguchi K, Koga S, Nishikido M: Systemic immune response after intravesical instillation of bacilli Calmette-Guerin (BCG) for superficial bladder cancer. *Clin Exp Immunol*, 115: 131-135, 1999.
7. Lamm DL: BCG immunotherapy for transitional cell carcinoma of the bladder, urethra, and upper urinary tract. *Midiguide to Urology*, 12: 1-8, 1999.
8. Dalbagni G, Rechtschaffen T, Herr HW: Is transurethral biopsy of the bladder necessary after 3 months to evaluate response to bacillus Calmette-Guerin therapy? *J Urol*, 162: 708-709, 1999.

Received: January 15, 2000

Accepted: January 25, 2000

Correspondence address:

Ralph W. deVere White, M.D.
Chairman, Department of Urology
UC Davis School of Medicine
4860 Y Street, Suite 3500
Sacramento, California, 95817, USA
Fax: ++ (1) (916) 734-8094
E-mail: rwdeverewhite@ucdavis.edu