Intravesical therapy for urothelial carcinoma of the bladder

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ABSTRACT

Transurethral resection is an effective therapy for non-muscle-invasive bladder cancer. However, the high rates of recurrence and significant risk of progression in higher grade tumors mandates additional therapy with intravesical agents. In this review we discuss the role of various intravesical agents currently in use including the immunomodulatory agent BCG and chemotherapeutic agents. We discuss the current guidelines and the role of these therapeutic agents in the context of higher grade Ta and T1 tumors.

Key words: Bladder, cancer, chemotherapy, intravesical

INTRODUCTION

Bladder cancer is estimated to be the ninth most common cause of cancer worldwide (357,000 cases in 2002). At diagnosis, 60–80% of bladder tumors are non-muscle invasive (NMIBC) and confined to the urothelium and/or lamina propria. These include papillary tumors, Ta (confined to urothelium) and T1 (lamina propria invasion) or carcinoma in situ (CIS), a flat erythematous lesion. A transurethral resection of the bladder tumor (TURBT) is the standard treatment for Ta and T1 bladder tumors and helps in establishing the diagnosis, staging and assigning a risk profile. For low-grade papillary (pTaG1) tumors TURBT may be the only treatment required. However, tumor recurrence is a major problem with higher grade Ta and T1 tumors. At 1 year following TURBT about 20% of patients with low-risk NMIBC and 40% of those with medium-risk NMIBC will develop tumor recurrence. Patients with high-risk NMIBC will express an even higher recurrence rate (90%) at 1-2 years following TURBT. In an effort to reduce the high recurrence rates adjuvant therapy with intravesical agents have been introduced.

Urinary bladder being an easily accessible organ is well suited for topical therapy. Hence it is not surprising that intravesical therapy has been extensively studied and utilized. The rationale for intravesical therapy is to maximize the exposure of tumors located in the bladder to therapeutic agents while limiting the systemic exposure. Depending on tumor and patient characteristics, a significant number of patients may benefit from intravesical therapy. Immunomodulatory agents mainly intravesical BCG and chemotherapeutic agents such as Mitomycin C are among the most commonly employed intravesical agents. Perioperative installation of chemotherapy immediately after TURBT is gaining increasing acceptance. The rationale for perioperative instillation includes the destruction of residual microscopic tumor at the site of TURBT and of circulating tumor cells, thereby preventing reimplantation. Intravesical therapy can also be given as a maintenance therapy as opposed to an induction course alone to provide long-term immunostimulation or local chemotoxicity aimed at preventing tumor recurrence.

RISK ASSESSMENT

NMIBC represents a wide range of tumor biology and behavior. Therefore, risk assessment is essential before employing intravesical therapy. Sylvester et al, have developed a prediction tool using data from seven European Organization of Research and Treatment of Cancer (EORTC) randomized clinical trials conducted between 1979 and 1989. In this risk assessment tool, risk factors are given
a score separately for recurrence and progression [Table 1].[8,9] The sum of all the risk factor scores is calculated separately for recurrence and progression [Table 2]. These final scores predict the probability of recurrence and progression at 1 and 5 years.

**INTRAVESICAL AGENTS**

Two groups of intravesical therapeutic agents are available. The immunotherapeutic agents include Bacillus Calmette-Guérin (BCG) and interferon. The most commonly used chemotherapeutic agents include Mitomycin C, Doxorubicin and more recently Gemcitabine.

**BACILLUS CALMETTE GUÉRIN**

BCG remains the most effective intravesical treatment for NMIBC. Intravesical BCG was introduced as a treatment for urothelial cancer of the bladder more than 30 years ago by Morales et al.[10] Since then several studies and meta-analysis have shown that TURBT followed by intravesical BCG is superior to TURBT alone as well as to TURBT plus intravesical chemotherapy for delaying time to first recurrence.[4,11-13]

The precise mechanism of action of BCG is not fully understood. Following the initial mycobacterial adherence to the urothelium, a complex immunological cascade is initiated and leads to a vigorous cellular immune response. Urinary cytokine patterns and the intensity of bladder wall infiltration with immune-competent cells have been studied to better define the number of doses and the time interval.[14] Zlotta et al, reported in their study that in most patients, the maximal peripheral immune response was already observed after four weekly instillations, although patients who were not previously immunized against mycobacterial antigens required six instillations to achieve maximum stimulation.[15] It has also been shown that the urinary cytokine levels peak at the third week after an induction course.[16]

A BCG induction course is typically started only after a minimum of 2 weeks following a TURBT to allow re-epithelization and to reduce the risk of systemic side effects. The current view is that the available stains do not differ in efficacy.[17] The dose of intravesical BCG was determined to be 120 mg (Frappier); however, in an effort to reduce the toxicity dose reduction has been proposed. One study reported that a three-fold reduction in dose is
### Table 3: Complications of Intravesical BCG therapy

| Complication                        | Association                                      | Suggested treatment                                                                 |
|-------------------------------------|--------------------------------------------------|-------------------------------------------------------------------------------------|
| **Minor**                          |                                                  |                                      |                                      |                                      |
| Dysuria and frequency              | Expected and common side effect 5-90% incidence  | R/O bacterial UTI by urine and blood culture                                      |
|                                    | 1-34% incidence                                  | If fever >102 F or lasts >48 hr needs antituberculous therapy                      |
|                                    | Generally seen on 2nd or 3rd instillation         | Typically self limiting                                                            |
|                                    |                                                  | Stop intravesical therapy till hematuria resolves                                  |
|                                    |                                                  | Urine C/S as needed                                                               |
|                                    |                                                  | If not resolved in 2-3 weeks cystoscopy to R/O persistent tumor                    |
| Hematuria                           |                                                  |                                      |                                      |                                      |
|                                    |                                                  |                                      |                                      |                                      |
| **Major**                          |                                                  |                                      |                                      |                                      |
| Fever                              | Nearly 3% incidence (>103 F)                     | Urine culture                                                                      |
|                                    |                                                  | Complete blood count and chest X-ray                                             |
|                                    |                                                  | Antipyretics and fluids                                                          |
|                                    |                                                  | Antibiotics as necessary and consider INH 300 mg once daily                        |
|                                    |                                                  | Intravesical therapy should be withheld until all adverse symptoms have resolved  |
|                                    |                                                  | and consideration should be given to decreased dose BCG and INH given at least   |
|                                    |                                                  | 1 day before treatment                                                            |
| Granulomatous prostatitis          | 1-40% incidence                                  | If symptomatic INH with RFP for 3 months                                           |
|                                    | Mostly asymptomatic                               |                                      |                                      |                                      |
| Granulomatous epididymoorchitis     | Infrequent complication                          | If fever or leucocytopenia                                                        |
|                                    | Local induration and pain                         | INH with RFP for 3-6 months                                                      |
| Granulomatous hepatitis or pneumonitis | <1% incidence                                   | INH with RFP for 6 months, add 1200 mg of Ethambutol if severely ill.             |
| BCG sepsis                         | Most serious and potentially fatal <0.4% incidence | Emergency hospital admission and treatment, possible intensive care management.     |
|                                    | Systemic absorption associated with traumatic catheterization or bladder inflammation | INH 300 mg daily                                                                  |
|                                    | Fever, chills, hypotension and mental dysfunction | RFP 600 mg daily                                                                 |
|                                    | Can progress to multi-organ dysfunction           | Ethambutol 1,200 mg daily                                                        |
|                                    |                                                  | Prednisolone 40 mg daily                                                          |
| Allergic reactions                 | Arthritis or migratory arthralgia in 0.5% of cases and skin rash in 0.3% | Do not necessitate discontinuing BCG in patients with high risk tumors.          |
|                                    |                                                  | Prophylactic INH and antihistamine control most symptoms                          |
| Ureteral obstruction                | Potentially serious complication is reported in 0.3% of patients CIS of the bladder and vesicoureteral reflux are probably predisposing factors. | Long-term antibiotics and postponement of further BCG therapy                     |
| Contracted bladder                 | less than 1%                                      | Treatment consists of withholding BCG and hydrodistention.                         |
|                                    | Patients on a maintenance schedule may be at higher risk | If conservative measures fail, cystectomy may be required.                        |

**as effective as the standard dose with significantly reduced toxicity even in high-risk NMIBC.**[18] The standard dwell time for intravesical BCG is 1-2 hours to allow good mycobacterial adhesion. However, the duration can be reduced as an alternative to dose reduction in patients with significant side effects.[19] A standard induction course consists of six weekly instillations. Maintenance is typically given as three weekly instillations at 3 and 6 months and then every 6 months for up to 3 years. At least a year of maintenance is recommended by European Association of Urologists (EAU) and American Urological association (AUA). Intravesical BCG is contraindicated under the following circumstances: a TURBT within the past 2 weeks, traumatic catheterization, hematuria, urethral stenosis, active tuberculosis, prior BCG sepsis and immunosuppression.

Intravesical BCG is recommended as an adjuvant therapy for intermediate-risk and high-risk NMIBC. The EAU and AUA guidelines recommend immediate instillation of chemotherapy followed by intravesical BCG with a maintenance schedule in high-risk NMIBC. In intermediate risk NMIBC BCG can be offered as an alternative to chemotherapy especially if chemotherapy is badly tolerated or if tumor recurs in spite of repeated chemotherapy instillations. The guidelines recommend that maintenance BCG should be given for at least 1 year.

Some of the complications of intravesical BCG therapy and management is shown in Table 3.[20]

**BCG efficacy**

Several studies have addressed the role of intravesical BCG as an adjuvant therapy to reduce recurrence following
TURBT. Patard et al.\(^{[21]}\) reported their retrospective case-control study on T1G3 tumors. The median tumor size was 20 mm, most had single tumor (58.8%) and CIS was found in six patients (7.5%). Thirty patients were treated with TURBT and 50 patients were treated with TURBT followed by BCG. The two groups of patients were comparable and followed up during a median time of 61 and 65 months, respectively (P=0.454). Patients with TURBT alone recurred (P=0.0001), progressed (P=0.040) and died (overall survival: P=0.009; disease-specific P=0.040) earlier than patients who received intravesical instillations of BCG. Shahin et al.\(^{[22]}\) in their retrospective experience reported that BCG delays recurrence and progression when compared to TURBT alone; however, it does not influence the overall or cause specific survival.

Several meta-analyses have shown that intravesical BCG is superior to intravesical chemotherapy, only if maintenance therapy is given. Shelley et al.\(^{[4]}\) reported their meta-analysis on medium- to high-risk Ta and T1. Six trials had sufficient data for meta-analysis and included 1527 patients, 693 in the mitomycin and B34 in the BCG arm. There was no significant difference between mitomycin C and BCG for tumour recurrence in the six trials, with a weighted mean log hazard ratio, (variance) of -0.022 (0.005). Only two trials included sufficient data to analyze disease progression and survival, representing 681 patients (338 randomized to BCG and 343 to mitomycin C). There was no significant difference between mitomycin C and BCG for disease progression (P = 0.16), or survival (P = 0.50). Tumor recurrence was significantly lower with intravesical BCG than with mitomycin C only in those patients at high risk of tumor recurrence. However, there was no difference in progression or survival. Bohle et al. performed a meta-analysis of 11 clinical trials, 1,421 patients were treated with BCG and 1,328 were treated with mitomycin C.\(^{[1]}\) Within the overall median follow-up time of 26 months 38.6% of the patients in the BCG group and 46.4% of those in the mitomycin C group had tumor recurrence. In seven of 11 studies BCG was significantly superior to mitomycin C, in three studies no significant difference was found, while in one study mitomycin C was significantly superior to BCG. An overall statistically significant superiority of BCG versus mitomycin C efficacy in reducing tumor recurrence was detected (OR 0.56, reported that BCG delays recurrence and progression when compared to TURBT alone; however, it does not influence the overall or cause specific survival.

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### Table 4: Practical aspects of intravesical chemotherapy

| Complication                  | Association                                                                 | Suggested treatment                                      |
|-------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------|
| Chemical cystitis             | Frequently encountered side effect of intravesical chemotherapy              | Oxybutynin, phenazopyridine, or propantheline bromide.    |
|                               | Seen in as many as 56% of doxorubicin-treated patients, 41% of mitomycin C (MMC) treated patients, and approximately one-third of epirubicin-treated subjects |                                                            |
| Hematuria                     | Seen in up to 40% of patients treated with intravesical chemotherapy.        | A urine culture is necessary to exclude bacterial cystitis and the instillations are deferred until the urine is clear. In the case of persistent hematuria a cystoscopy should be performed to rule out residual tumor. |
| Contracted bladder            | Occurs due to extravasation of the intravesical therapeutic agents and is a serious complication. This is usually associated with multiple TURBTs and maintenance instillations. | Cystoprostatectomy with orthotopic neobladder reconstruction may be the optimal solution to alleviate severe lower urinary tract symptoms and to remove the risk of subsequent urothelial malignancy. |
| Contact dermatitis            | Reported in up to 10% of patients treated with intravesical MMC and often leads to eczema-like desquamation of the skin on the palms, soles, perineum, chest and face | Careful cleansing of the hands after drug-handling and cleansing of the genitals and perineum after voiding may help prevent contact dermatitis associated with intravesical MMC. Requires cessation of therapy. The use of topical steroid creams usually relieves the symptoms. |
| Bladder wall calcifications   | Occasionally result following administration of intravesical mitomycin C   | They rarely cause symptoms.                               |
| Myelosuppression              | Very rarely noted in patients treated with mitomycin C and may result from the use of high-concentration instillations in a recently traumatized bladder | Cessation of intravesical chemotherapy and close monitoring of the white blood cell count. |

### Table 5: Complications of intravesical chemotherapy

- Chemical cystitis: Frequently encountered side effect of intravesical chemotherapy. Seen in as many as 56% of doxorubicin-treated patients, 41% of mitomycin C (MMC) treated patients, and approximately one-third of epirubicin-treated subjects. Suggested treatment: Oxybutynin, phenazopyridine, or propantheline bromide.
- Hematuria: Seen in up to 40% of patients treated with intravesical chemotherapy. Suggested treatment: A urine culture is necessary to exclude bacterial cystitis and the instillations are deferred until the urine is clear. In the case of persistent hematuria a cystoscopy should be performed to rule out residual tumor.
- Contracted bladder: Occurs due to extravasation of the intravesical therapeutic agents and is a serious complication. This is usually associated with multiple TURBTs and maintenance instillations. Suggested treatment: Cystoprostatectomy with orthotopic neobladder reconstruction may be the optimal solution to alleviate severe lower urinary tract symptoms and to remove the risk of subsequent urothelial malignancy.
- Contact dermatitis: Reported in up to 10% of patients treated with intravesical MMC and often leads to eczema-like desquamation of the skin on the palms, soles, perineum, chest and face. Suggested treatment: Careful cleansing of the hands after drug-handling and cleansing of the genitals and perineum after voiding may help prevent contact dermatitis associated with intravesical MMC. Requires cessation of therapy. The use of topical steroid creams usually relieves the symptoms.
- Bladder wall calcifications: Occasionally result following administration of intravesical mitomycin C. Suggested treatment: They rarely cause symptoms.
- Myelosuppression: Very rarely noted in patients treated with mitomycin C and may result from the use of high-concentration instillations in a recently traumatized bladder. Suggested treatment: Cessation of intravesical chemotherapy and close monitoring of the white blood cell count.
The benefit of an immediate single instillation of BCG over mitomycin C (OR 0.43, 95% CI 0.35 to 0.53, \( P < 0.001 \)). Results suggest a significant superiority of BCG over mitomycin C in the prevention of tumor recurrences in the combined data and particularly in the BCG maintenance treatment subgroup, irrespective of the actual (intermediate or high) tumor risk status. The toxicity with BCG was higher but does not differ between BCG maintenance and non-maintenance groups.

More recent meta-analysis by Malmstrom et al, analyzed nine trials that included 2820 patients were identified. Overall, there was no difference in the time to first recurrence \( (P = 0.09) \) between BCG and MMC. In the trials with BCG maintenance, a 32% reduction in risk of recurrence on BCG compared to MMC was found \( (P < 0.0001) \), while there was a 28% risk increase \( (P = 0.006) \) for BCG in the trials without maintenance. BCG with maintenance was more effective than MMC in both patients previously treated and those not previously treated with chemotherapy. For prophylaxis of recurrence, maintenance BCG is required to demonstrate superiority to MMC. Prior intravesical chemotherapy was not a confounder. There were no statistically significant differences regarding progression, overall survival and cancer-specific survival between the two treatments.

Some meta-analyses have shown a reduction in progression with BCG,\cite{11,17} while others did not.\cite{4,13,23} A benefit if at all was shown only with maintenance BCG for 1 year or more. The AUA meta-analysis did not show a reduction in progression.\cite{23}

In summary a recent literature review by Gontero et al,\cite{24} reported that “BCG is the most effective intravesical agent for preventing NMIBC recurrence, but its role in progression remains controversial. In intermediate risk NMIBC, the superiority of BCG over chemotherapy is well established for recurrence but not for progression and needs to be balanced against higher toxicity. With regard to high-risk NMIBC, there is sufficient evidence to show that BCG is the most effective treatment of CIS for ablation, disease-free interval and progression, but the impact of BCG on the natural history of T1G3 tumors relies on a low level of evidence. Maintenance remains crucial for efficacy.”

**INTERFERON**

Interferons are natural glycoproteins that mediate host immune responses such as the stimulation of phagocytes, inhibition of nucleotide synthesis, upregulation of tumor antigens, cytokine release, enhanced natural killer cell activity and activation of T and B lymphocyte.\cite{25} Among the subtypes, interferon-α has been the most extensively studied. Its efficacy is dose dependent.\cite{26,27} Interferon as a solitary agent is more expensive and less effective than BCG or intravesical chemotherapy in eradicating residual tumor, preventing recurrence of papillary tumor and treating CIS (20-43% complete response). As a prophylactic agent, interferon alone demonstrated recurrence rates that were generally inferior to those of BCG alone.\cite{28,29} Although it can be occasionally be effective in patients who have failed BCG with 15-20% complete response.

Interferon-α has also been studied in combination with either chemotherapy or BCG.\cite{30,31} However, there are no data to demonstrate superior efficacy of BCG with interferon compared with BCG alone as initial treatment, and BCG remains standard therapy for frontline management of high-risk NMIBC.

**INTRAVESICAL CHEMOTHERAPY**

The objective of intravesical chemotherapy is to eradicate microscopic residual tumor, prevent tumor recurrence and progression. An ideal intravesical agent should have minimal systemic absorption and maximum efficacy.\cite{32} The absorption and effectiveness of the drug is determined by physiochemical properties of the drug, physiological variables in urine and tissue pharmacokinetics.\cite{33,34} The absorption and efficacy can be modified by increasing the dose of the drug, decreasing dosing volume, increasing the contact time, decreasing urine production, maximizing bladder emptying and altering the pH.\cite{34}

**Indications**

According to AUA, EAU and Société Internationale d’Urologie (SIU) guidelines, intravesical chemotherapy is recommended as single immediate instillation after a TURBT and also as 6-12 weekly prophylactic course for intermediate risk tumors.\cite{9,23,35}

**Single perioperative instillation**

Both the EAU and AUA guidelines advocate the use of an immediate, single-instillation of intravesical chemotherapy following TURBT.\cite{9,23,36,37} The EORTC meta-analysis found no significant differences in efficacy among the chemotherapeutic agents studied. Therefore, choice of agent is left to the physician.\cite{38}

The time period within which the instillation is completed is very important. In all the studies included in the EORTC meta-analysis, the instillation was administered within 24 h.\cite{16} Kaasinen et al, reported that the risk of recurrence is twice when the instillation was not given within 24 h of TURBT.\cite{39} However, an immediate, single instillation of chemotherapy should be avoided when intra- or extraperitoneal perforation of the bladder is suspected.\cite{39} The benefit of an immediate single instillation of chemotherapy has not been proven in high grade NMIBC.
Induction cycle
The EAU and AUA guidelines suggest that intravesical chemotherapy or BCG should be offered to patients with intermediate-risk NMIBC following complete TURBT and a single, immediate instillation of chemotherapy. A meta-analysis conducted by the EORTC and the Medical Research Council found that adjuvant chemotherapy after TURBT significantly improves disease-free survival compared to TURBT alone. Review of controlled trials showed a mean decrease in tumor recurrence by 14%. However, there is no evidence that adjuvant chemotherapy delays progression.

Maintenance therapy
An EORTC randomized study demonstrated that 1 year of monthly maintenance and 6 months of monthly maintenance chemotherapy had similar efficacy in reducing recurrence rate when the first instillation was given immediately after TURBT. A review of clinical trials on intravesical chemotherapeutic instillations for NMIBC suggested that a short intensive schedule of instillations within the first 3-4 months following an immediate instillation is as effective as longer term treatment schedules. The authors suggested that use of long-term instillations for 1 year should only be considered when an immediate instillation has not been performed.

Practical considerations
Some practical considerations for administering intravesical chemotherapy are shown in Table 4. Some of the common complications of intravesical chemotherapy and their management is shown in Table 5.

Chemotherapeutic agents
Mitomycin
Mitomycin C is a 334-kD alkylating agent that inhibits DNA synthesis. MMC has an intracellular effect resulting in the production of an alkylating agent. The mode of action is poorly understood. The dose varies between 20 and 80 mg per instillation. It is most commonly given as 40 mg in 40 mL of saline or sterile water administered weekly for 8 weeks followed by monthly instillations for one year. The most common side effects are frequency, chemical cystitis and allergic skin reactions due to contact dermatitis.

MMC is primarily administered as a single perioperative instillation and less frequently given weekly for 6-8 weeks after a TURBT. Data from the EORTC meta-analysis of 23 studies have confirmed that the average net benefit for single perioperative MMC is about 14% at 1-3 years and 7% at 7 years. Lamm et al, performed a meta-analysis of five controlled trials and reported that the recurrence rate was reduced by 15%. The advantage of MMC was 15% (52% recurrences in the control groups versus 37% in the MMC group). A long-term effect on recurrence and disease progression was not demonstrated. In an EORTC marker lesion study (30864), the complete response rate for the marker lesion after eight instillations with 80 mg of MMC was 50%. The 6 and 9 weekly instillation when compared with 6 weekly BCG-RIVM had similar disease-free percentage for pTa, pT1 and CIS. A meta-analysis of nine trials with a median follow-up of 26 months found similar recurrence rate for BCG (7.67%) and MMC (9.44%). Huncharek and Kupelnik reported a meta-analysis of 2427 patients, examining the endpoint of progression in eight clinical trials, and found no clear advantage for BCG over intravesical chemotherapy.

Huland et al, compared 3-year MMC instillation therapy (42 instillations of 20 mg) to no intravesical therapy in a randomized trial after complete TURBT and found a recurrence rate as low as 10.2% when compared with a control group 51%. Recently a study showed that long-term maintenance with MMC was associated with a significant reduction in recurrence rates compared to short-course therapy. Malmstrom et al, found that maintenance BCG was superior in preventing recurrence compared to maintenance MMC, although no difference was found for progression and survival.

Recently there have been suggestions that the efficacy of MMC can be improved by altering the delivery methods. This can be achieved by eliminating residual urine volume, overnight fasting, using sodium bicarbonate to alkalinize the urine thereby reducing drug degradation, and increasing concentration to 40 mg in 20 mL. Addition of local microwave therapy to MMC, 20 mg/50 mL reduced the recurrence rates from 57 to 17% in a multicenter trial. Electromotive intravesical MMC appears to improve drug delivery into bladder tissue and reduces recurrence rates from 58 to 31%.

Guide lines
In patients at low risk of tumor recurrence and progression immediate instillation of single dose of chemotherapy is recommended as the adjuvant treatment. In patients at intermediate or high risk of recurrence, one immediate instillation of chemotherapy followed by further instillations of chemotherapy or BCG for a minimum of 1 year.

Adriamycin
Adriamycin (Doxorubicin, ADM) is a 580-kD anthracycline antibiotic that acts by binding DNA base pairs, inhibiting topoisomerase II, and inhibiting protein synthesis. The response rates of up to 56% have been reported when ADM was used as treatment for papillary tumors, while for CIS the response was only 34%. The most frequent side effect of ADM is chemical cystitis, seen in 25-30% of the patients. Rare side effects are allergic reactions (0.3%), gastrointestinal side effects (1.7%) and fever (0.8%).
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**Epirubicin**

Epirubicin (EPI) exerts a similar antitumor action as ADM.\[58\] With a molecular weight of 544 kD its absorption is very limited.\[59\] The most frequent side effect is chemical cystitis, seen in about of patients.\[60\] Most studies have shown that perioperative epirubicin reduces the recurrence rate by 13-27%.\[61-63\] Maintenance therapy has shown benefit in some studies; however, most of them showed no significant benefit.\[44,64-68\]

**Valrubicin**

Valrubicin (AD32) is a N-trifluoroacetyl, 14-valerate derivative of the anthracycline ADM.\[69\] Valrubicin is the only drug approved by the USA Food and Drug Administration for BCG refractory CIS, in patients who refuse surgery or are medically unfit to undergo surgery. The initial reported complete response rate was 21%; however, only 8% of patients remained tumor-free at the last evaluation.\[70\] In a prospective phase II marker lesion study, 40 patients with TCC underwent a deliberately incomplete TURBT leaving a tumor <1cm in diameter in the bladder. Fifty-four percent had a complete response.\[71\] The most commonly reported adverse effects were dysuria (77%), hematuria (59%) and urgency/frequency (23%).\[72\]

**Gemcitabine**

Gemcitabine is a new deoxycytidine analogue with a broad spectrum antitumor activity. It has a molecular weight of 299 kD and after intracellular activation, the active metabolite is incorporated into DNA, resulting in DNA synthesis inhibition.\[73\] The molecular weight of gemcitabine is lower than other intravesical chemotherapeutic agents including MMC (389 kD) and doxorubicin (589 kD). This will enable better penetration into the bladder mucosa. However, it is also large enough to avoid significant systemic absorption in an intact bladder.\[73\] The typical dose is 2000 mg of gemcitabine in 50 or 100 mL normal saline, administered intravesically for up to 2 h and additional doses once a week for 6 week has been well tolerated.\[74\] Mild transient urgency is seen in 12-26% and rarely leucopenia.

Intravesical gemcitabine has been tested in several phase I studies.\[74,75\] In phase II studies on a marker lesion in intermediate-risk Ta/T1 bladder cancer intravesical gemcitabine showed complete response in up to 60% of patients.\[76\] A favorable profile in prophylaxis was confirmed in another phase II, single-arm, multicentric Italian experience.\[49\] In high-risk NMIBC, intravesical gemcitabine has shown unexpected complete responses in CIS refractory to BCG in some studies. Initial activity was substantial; 50% of the patients achieved a CR, and 23% demonstrated a partial response. Initial trials have also documented “clinically relevant” responses in prophylaxis.\[77,78\] Thirty-four patients with low- to intermediate-risk solitary or multiple lesions less than 2 cm received four weekly instillations of gemcitabine 2000 mg in a neoadjuvant setting.\[79\]

**Apaziquone**

Apaziquone (EO9) (Spectrum Pharmaceuticals Inc., Irvine, CA) is a novel indolequinone derivative of MMC. The enzyme deoxymethylidione- diaphorase which is found in 40% of bladder tumors activates EO9. The normal bladder tissue lacks this enzyme and hence does not activate EO9 thus decreasing toxicity.\[38,80\] Van der Heijden et al.\[40\] performed a phase II marker lesion study on patients with Ta–T1 G1–G2 NMIBC undergoing TURBT, with six weekly 4 mg/40 mL EO9 and a complete response of 67%.\[81\]

**CONCLUSIONS**

The type of intravesical therapy is chosen based on the risk profile. Following a TURBT, the low-risk group should receive single immediate instillation of chemotherapy. Intermediate risk group should receive single immediate instillation of chemotherapy with additional therapy of either further instillations of chemotherapy or intravesical BCG with maintenance of at least 1 year. High-risk group should receive single immediate instillation of chemotherapy and intravesical BCG with maintenance of at least 1 year. Immediate cystectomy should be considered in patients with high risk, when the risk of progression is high or in the event of BCG failure.

**REFERENCES**

1. Parkin DM. The global burden of urinary bladder cancer. Scand J Urol Nephrol Suppl 2008;218:12-20.
2. O’Donnell MA. Practical applications of intravesical chemotherapy and immunotherapy in high-risk patients with superficial bladder cancer. Urol Clin North Am 2005;32:121-31.
3. Adiyat KT, Katkoori D, Soloway CT, De los Santos R, Manoharan M, Soloway MS. Complete transurethral resection of bladder tumor: Are the guidelines being followed? Urology 2010;75:365-7.
4. Shelley MD, Wilt TJ, Court J, Coles B, Kynaston H, Mason MD. Intravesical bacillus Calmette-Guerin is superior to mitomycin C in reducing tumour recurrence in high-risk superficial bladder cancer: A meta-analysis of randomized trials. BJU Int 2004;93:485-90.
5. Sylvester RJ, Oosterlinck W, van der Meijden AP. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: A meta-analysis of published results of randomized clinical trials. J Urol 2004;171:2186-90.
6. Weldon TE, Soloway MS. Susceptibility of urothelium to neoplastic cellular implantation. Urology 1975;5:824-7.
7. Soloway MS. Rationale for intensive intravesical chemotherapy for superficial bladder cancer. J Urol 1980;123:461-6.
8. Sylvester RJ, van der Meijden AP, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: A combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006;49:466-5.
9. Babjuk M, Oosterlinck W, Sylvester R, Kaasinen E, Bohle A, Palou-Redorta J. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder. Eur Urol 2008;54:303-14.
10. Morales A, Eidinger D, Bruce AW. Intracavitary bacillus calmette-guerin in the treatment of superficial bladder tumors. J Urol 1976;116:180-3.
11. Bohle A, Jocham D, Bock PR. Intravesical bacillus Calmette-Guérin versus mitomycin C for superficial bladder cancer: A formal meta-analysis of comparative studies on recurrence and toxicity. J Urol 2003;169:90-5.

12. Han RF, Pan JC. Can intravesical bacillus Calmette-Guérin reduce recurrence in patients with superficial bladder cancer? A meta-analysis of randomized trials. Urology 2006;67:1216-23.

13. Malmström PU, Sylvester RJ. An individual patient data meta-analysis of the long-term outcome of randomized studies comparing intravesical mitomycin C versus bacillus Calmette-Guérin for non-muscle-invasive bladder cancer. Eur Urol 2009;56:247-56.

14. Brandau S, Suttmann H. Thirty years of BCG immunotherapy for non-muscle invasive bladder cancer: A success story with room for improvement. Biomod Pharmacother 2007;61:299-305.

15. Zlotra AR, van Vooren JP, Huygen K, Drowart A, Decock M, Pirson P, et al. What is the optimal regimen for BCG intravesical therapy? Are six weekly instillations necessary? Eur Urol 2000;37:470-7.

16. Sylvester RJ, van der Meijden A, Witjes JA, Jakse G, Nonomura N, Cheng C, et al. High-grade Ta urothelial carcinoma and carcinoma in situ of the bladder. Urology 2005;66:90-107.

17. Sylvester RJ, van der MA, Lamm DL. Intravesical bacillus Calmette-Guérin reduces the risk of progression in patients with superficial bladder cancer: A meta-analysis of the published results of randomized clinical trials. J Urol 2002;168:164-70.

18. Martínez-Piñeiro JA, Martínez-Piñeiro L, Solsena E, Rodríguez RH, Gómez JM, Martin MG, et al. Has a 3-fold decreased dose of bacillus Calmette-Guérin the same efficacy against recurrences and progression of TaG3 and Tis bladder tumors than the standard dose? Results of a prospective randomized trial. J Urol 2005;174:1242-7.

19. Andius P, Fehring M, Holmang S. Intravesical bacillus Calmette-Guérin therapy: Experience with a reduced dwell-time in patients with pronounced side-effects. BJU Int 2005;96:1290-3.

20. Koya MP, Simon MA, Soloway MS. Complications of intravesical therapy for urothelial cancer of the bladder. J Urol 2006;175:2004-10.

21. Patard JJ, Rodriguez A, Leray E, Rioux-Leclercq N, Guille F, Lobel B. Intravesical Bacillus Calmette-Guérin treatment improves patient survival in T1G3 bladder tumours. Eur Urol 2002;41:635-41.

22. Shahin O, Thalmann GN, Rentsch C, Mazzucchelli L, Studer UE. A retrospective analysis of 153 patients treated with or without intravesical bacillus Calmette-Guérin for primary stage T1 grade 3 bladder cancer: Recurrence, progression and survival. J Urol 2003;169:96-100.

23. Hall MC, Chang SS, Dalbagni G, Pruthi RS, Seigle JD, Skinner EC, et al. Guideline for the management of nonmuscle invasive bladder cancer (stages Ta, T1, and Tis): The American Urological Association. J Urol 1999;162:1697-701.

24. Gontero P, Bohle A, Malmström PU, O'Donnell MA, Oderda M, Sylvester R, et al. The role of bacillus Calmette-Guérin in the treatment of non-muscle-invasive bladder cancer. Eur Urol 2010;57:410-29.

25. Naito K, Hisazumi H, Uchibayashi T, Amano T, Hirata A, Komatsu K, et al. Intravesical Bacillus Calmette-Guérin treatment improves patient outcome in patients with superficial bladder cancer. Urology 2005;66:75-89.

26. Shahin O, Thalmann GN, Rentsch C, Mazzucchelli L, Studer UE. Intravesical Bacillus Calmette-Guérin reduces the risk of progression in patients with superficial bladder cancer: A meta-analysis of the published results of randomized clinical trials. J Urol 2005;174:1242-7.

27. Martínez-Piñeiro JA, Martínez-Piñeiro L, Solsena E, Rodríguez RH, Gómez JM, Martin MG, et al. Has a 3-fold decreased dose of bacillus Calmette-Guérin the same efficacy against recurrences and progression of TaG3 and Tis bladder tumors than the standard dose? Results of a prospective randomized trial. J Urol 2005;174:1242-7.

28. Andius P, Fehring M, Holmang S. Intravesical bacillus Calmette-Guérin therapy: Experience with a reduced dwell-time in patients with pronounced side-effects. BJU Int 2005;96:1290-3.

29. Koya MP, Simon MA, Soloway MS. Complications of intravesical therapy for urothelial cancer of the bladder. J Urol 2006;175:2004-10.

30. Patard JJ, Rodriguez A, Leray E, Rioux-Leclercq N, Guille F, Lobel B. Intravesical Bacillus Calmette-Guérin treatment improves patient survival in T1G3 bladder tumours. Eur Urol 2002;41:635-41.

31. Shahin O, Thalmann GN, Rentsch C, Mazzucchelli L, Studer UE. A retrospective analysis of 153 patients treated with or without intravesical bacillus Calmette-Guérin for primary stage T1 grade 3 bladder cancer: Recurrence, progression and survival. J Urol 2003;169:96-100.

32. Hall MC, Chang SS, Dalbagni G, Pruthi RS, Seigle JD, Skinner EC, et al. Guideline for the management of nonmuscle invasive bladder cancer (stages Ta, T1, and Tis): The American Urological Association. J Urol 1999;162:1697-701.

33. Gontero P, Bohle A, Malmström PU, O’Donnell MA, Oderda M, Sylvester R, et al. The role of bacillus Calmette-Guérin in the treatment of non-muscle-invasive bladder cancer. Eur Urol 2010;57:410-29.

34. Naito K, Hisazumi H, Uchibayashi T, Amano T, Hirata A, Komatsu K, et al. Intravesical Bacillus Calmette-Guérin reduces the risk of progression in patients with superficial bladder cancer: A meta-analysis of the published results of randomized clinical trials. J Urol 2005;174:1242-7.

35. Martínez-Piñeiro JA, Martínez-Piñeiro L, Solsena E, Rodríguez RH, Gómez JM, Martin MG, et al. Has a 3-fold decreased dose of bacillus Calmette-Guérin the same efficacy against recurrences and progression of TaG3 and Tis bladder tumors than the standard dose? Results of a prospective randomized trial. J Urol 2005;174:1242-7.
Long-term follow-up of an EORTC randomized pilot study of the tolerability and toxicity of intravesical instillations of mitomycin-C, BCG-Tice, and BCG-RIVM in pTa-pT1 tumours and primary carcinoma in situ of the urinary bladder: Dutch South-East Cooperative Urological Group. Eur J Cancer 1993;29A:1672-6.

50. Huncharek M, Kulpelnick B. The influence of intravesical therapy on progression of superficial transitional cell carcinoma of the bladder: A metaanalytic comparison of chemotherapy versus bacilli Calmette-Guerin immunotherapy. Am J Clin Oncol 2004;27:522-8.

51. Huland H, Klöppel G, Feddersen I, Otto U, Brachmann W, Hubmann H, et al. Comparison of different schedules of cytostatic intravesical instillations in patients with superficial bladder carcinoma: Final evaluation of a prospective multicenter trial with 419 patients. J Urol 1990;144:68-71.

52. Richie JP. Intravesical chemotherapy: Treatment selection, techniques, and results. Urol Clin North Am 1992;19:521-7.

53. Malmstrom PJ, Wijkstrom H, Lundholm C, Wester K, Busch C, Norlen BJ. 5-year followup of a randomized prospective study comparing mitomycin C and bacillus Calmette-Guerin in patients with superficial bladder carcinoma: Swedish-Norwegian Bladder Cancer Study Group. J Urol 1999;161:1124-7.

54. Au JL, Badalament RA, Wientjes MG, Young DC, Warner JA, Venema PL, et al. Methods to improve efficacy of intravesical mitomycin C: Results of a randomized phase III trial. J Natl Cancer Inst 2001;93:597-604.

55. Di Stasi SM, Giannantoni A, Stephen RL, Capelli G, Navarra P, Massoud R, et al. Intravesical electromotive mitomycin C versus passive transport mitomycin C for high risk superficial bladder cancer: A prospective randomized study. J Urol 2003;170:777-82.

56. Lamm DL, Blumenstein BA, Crawford ED, Montie JE, Scardino P, Grossman HB, et al. A randomized trial of intravesical doxorubicin and immunotherapy with bacilli Calmette-Guerin for transitional-cell carcinoma of the bladder. N Engl J Med 1991;325:1205-9.

57. Thrasher JB, Crawford ED. Complications of intravesical chemotherapy. Urol Clin North Am 1992;19:529-39.

58. Onrust SV, Wiseman LR, Goa KL. Epirubicin: A review of its intravesical use in superficial bladder cancer. Drugs Aging 1999;15:69-75.

59. Laufer M, Ramalingam S, Schoenberg MP, Haisfield-Wolf ME, Zuhowski EG, Trueheart IN, et al. Intravesical gemcitabine therapy for superficial transitional cell carcinoma of the bladder: A phase I and pharmacokinetic study. J Clin Oncol 2003;21:697-703.

60. Dalbagni G, Russo P, Sheinfeld J, Mazumdar M, Tong W, Rabbani F, et al. Phase I trial of intravesical gemcitabine in bacillus Calmette-Guerin-refractory transitional-cell carcinoma of the bladder. J Clin Oncol 2002;20:3193-8.

61. Ontero P, Fiorito C, Lucca I, Valentino F, Tizzani A. New drugs currently available in non-muscle invasive bladder cancer: Update on gemcitabine studies. Arch Ital Urol Androl 2008;80:162-6.

62. Lauffer M, Ramalingam S, Schoenberg MP, Haisfield-Wolf ME, Zuhowski EG, Trueheart IN, et al. Intravesical gemcitabine therapy for superficial transitional cell carcinoma of the bladder: A phase I and pharmacokinetic study. J Clin Oncol 2003;21:697-703.

63. Mohanty NK, Nayak RL, Vasudeva P, Arora RP. Intravesicle gemcitabine in management of BCG refractory superficial TCC of urinary bladder-our experience. Urol Oncol 2008;26:616-9.

64. Maffeizini M, Campodonico F, Canepa G, Cartabeni G, Fontana V. Short-schedule intravesical gemcitabine with ablative intent in recurrent Ta-T1, G1-G2, low- or intermediate-risk, transitional cell carcinoma of the bladder. Eur Urol 2007;51:956-61.

65. Li D, Gan Y, Wientjes MG, Badalament RA, Au JL. Distribution of DT-diaphorase and reduced nicotinamide adenine dinucleotide phosphate: Cytochrome p450 oxidoreductase in bladder tissues and tumors. J Urol 2001;166:2500-5.
81. van der Heijden AG, Moonen PM, Cornel EB, Vergunst H, de Reijke TM, van Boven E, et al. Phase II marker lesion study with intravesical instillation of apaziquone for superficial bladder cancer: Toxicity and marker response. J Urol 2006;176:1349-53.

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