Basrah Journal Of Surgery

Bas J Surg, March, 18, 2012

EFFICACY OF SEQUENTIAL BCG AND MITOMYCIN VERSUS MITOMYCIN ALONE FOR TREATMENT OF SUPERFICIAL BLADDER CANCER

Hazim R Akal
FICMS (Urol.), Assistant Prof., Dept.of Surgery, Medical College, Thiqar University

A study to compare the efficacy and local toxicity of combining anticancer drugs immunotherapy and chemotherapy (Sequential BCG and mitomycin c) versus mitomycin alone in the treatment of superficial bladder cancer after complete transurethral resection.

The study was designed as a prospective study done in Al-hussain Teaching Hospital in Thiqar from July 2007 to August 2010. After transurethral resection and multiple biopsies, eighty-three patients (62m, 21f) from 38-75 years old, suffering from primary superficial (Ta-T1) TCC of the bladder, were randomly assigned to receive intravesical instillations of Mitomycin C (MMC) alone for 41 patients, and the sequential BCG and Mitomycin c, for 42 patients (81 mg BCG infused over 120 min once a week for 2 weeks, followed by 40 mg Mitomycin c once a week for four weeks.

The patients evaluated for complications and recurrence and progression rate, they have follow up cystoscope every 3 months for the 1st year then every 6 months for the 2nd year and then yearly . Mean follow-up time was 36 months. The main object of the study were evaluation of recurrence and progression rate and estimate the safety with evaluation of subjective and objective side effects and clinical complications.

Of the 83 randomly assigned patients, the analysis demonstrated a significant statistical difference in the recurrence rate. Patients assigned sequential BCG and Mitomycin c had lower recurrence rate 16.6 % (7 patients) versus 29.2% (12 patients) in those assigned for Mitomycin c alone, the difference between groups 12.6%; The progression rate in patients assigned sequential BCG and Mitomycin c about 7 % (3 patients) versus 17 % (7 patients) in those assigned for Mitomycin c alone, the difference between groups 10%. However the side-effects were mainly localized to the bladder, the complications after the treatment more common in patients receive sequential BCG and Mitomycin c than in those receive Mitomycin c alone.

Cystitis occur in about 35 patients (83%) in those receiving sequential BCG and Mitomycin c, and two patient 4.7 % developed fever and chills. While in patients receive Mitomycin alone the complications were less cystitis in 4 patients 10%, rash in about 3 patients (7%) and myelosuppression two patients 5%.

Conclusion: In this series, sequential BCG and Mitomycin c appears to be more effective than Mitomycin c alone in the treatment of superficial bladder tumors at 36-month follow-up, despite an increased but acceptable local toxicity.This probably because the BCG-induced inflammation might increase the permeability of the bladder mucosa such that Mitomycin c can reach the target tissue more easily and exert its anticancer effect.

Introduction

Bladder cancer is the second most common cancer of the genitourinary tract. It accounts for 7% of new cancer cases in men and 2% of new cancer cases in women[1]. Patients typically present with either microscopic or gross hematuria. Bleeding from a bladder tumor is generally intermittent. Therefore resolution, either spontaneously or after antibiotic treatment for presumed bladder infection, does not reduce the need for urologic evaluation[2]. The average age at diagnosis is 65 years. 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[3,4]. 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[5,6]. 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[5]. 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[6,7]. 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[7].

Intravesical agent

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[8].

Bacillus Calmette Guerin: 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[9,10].

Cytotoxic chemotherapy directly kills cancer cells, while immunotherapy generally stimulates the patient's immune response. Increasing the dose of chemotherapy Results in increased cancer cell killing. However, increasing immunotherapy beyond the effective dose will begin to suppress the patient's immune response[11,12].

BCG, or bacillus Calmette-Guerin, is an attenuated form of the bacterium Mycobacterium tuberculosis, used to prevent tuberculosis. It is a potent immune stimulant. The standard dose of BCG is 81 mg for TheraCys® and 50 mg for TICE,® both in 50 cc physiologic saline. Treatment should be postponed for at least 1 to 2 weeks following tumor resection or bladder biopsy. A purified protein derivative (PPD) test may be performed as the response and side effects[13,14]. 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[15]. 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. 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 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)[20,21].

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[22,23]. 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[24,25]. Some of the complications of intravesical BCG therapy are minor and common like dysuria and frequency if sever patient may developed hematuria. Other complications are major but rare like fever, granulomatous prostatitis, granulomatous epididymoorchitis and even BCG sepsis[26]. In summary a recent literature review by Gontero et al, 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[27,28].

Intravesical chemotherapy

In contrast to systemic chemotherapy, where the administered dose is of primary importance, with topical intravesical chemotherapy, response is proportional to drug concentration and duration of exposure. Since duration of exposure is limited by bladder capacity, and increased urine output reduces drug concentration, overnight dehydration is recommended prior to drug instillation. Patients are generally asked to retain the instilled drug for 2 hours. Care must be taken to completely empty the bladder prior to

instilling chemotherapy[29,30]. An ultrasound of the bladder after insertion of a catheter is useful in confirming complete emptying, since, surprisingly, catheterization does not reliably empty. It resulted in a protocol that required confirmation of bladder emptying with a bladder scan prior to intravesical mitomycin instillation into the bladder for all patients[31,32]. They recommend that patients lie prone for 15 minutes to displace the air bubble introduced with the catheter, thereby ensuring contact at the bladder dome[33].

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[34]. The absorption and effectiveness of the drug is determined by physiochemical properties of the drug, physiological variables in urine and tissue pharmacokinetics[35]. 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[36]. 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[37,38].

Chemotherapeutic agents

Mitomycin C: 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 main side effects are skin rash, irritative bladder symptoms, bladder calcifications, and myelosuppression[39,40]. Contraindications of mitomycin include hypersensitivity, bladder perforation, myelosuppression & thrombocytopenia[41].

In a randomized study, recurrence was nearly cut in half by using an optimized schedule: 40 mg/20 cc (compared with 20 mg/20 cc), overnight dehydration, ultrasound-confirmed complete bladder emptying, alkalinization using 1.3 g of sodium bicarbonate the night before, morning of, and 30 minutes prior to treatment. Mitomycin C is inactivated by acid urine[42].

Recent studies also suggest that local hyperthermia, which can be obtained with a microwave applicator inserted into the bladder with a special catheter, can also enhance the efficacy of mitomycin C, albeit with a significant increase in systemic absorption. Myelosuppression is the primary systemic toxicity of mitomycin[43].

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[52]. 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[44]. 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[45]. 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%[45]. 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[46,47]. 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[48].

Patients and methods

The study was designed as a prospective study done in Al-hussain teaching hospital in Thiqar from July 2007 to august 2010. After transurethral resection and multiple biopsies , eighty-three patients suffering from primary superficial (Ta-T1) TCC of the bladder, were randomly assigned to receive intravesical instillations of mitomycin C (MMC) alone for 41 patients, and the sequential BCG and mitomycin, for 42 patients(81 mg BCG infused over 120 min once a week for 2 weeks, followed by 40 mg mitomycin once a week for four weeks. The patients evaluated for complications and recurrence rate they have follow up cystoscope every 3 months for the 1st year then every 6 months for the 2nd year and then yearly average fallow up time was 36 months. The main object of the study were evaluation of recurrence and progression rate and estimate the safety with evaluation of subjective and objective side effects and clinical complications. Mean follow-up time was 36 months

	TaG2	TaG3	T1G1	T1G2	T1G3
BCG + mitomcine group	3	14	10	8	7
Mitomycin group	4	12	9	8	8
Total	7	26	19	16	15

	Single	Multiple	< 3cm	>3cm
BCG + Mitomcin group	34	8	16	26
Mitomycin Group	32	9	15	26
Total	66	17	31	52

Patient eligible to either therapy should be evaluated thoroughly. History and physical examination to exclude any hypersensitivity to the instilled drug, recent hematuria or traumatic catheterization. History of BCG sepsis, repeated infection or any sign and symptom of immunosuppression. Investigation specially hematological assessment before every MMC session to exclude myelosuppression. A proper catheterization using 3-way catheter attached to an irrigant fluid, which kept turned off. Emptying of urinary bladder to decrease dilution effect of urine, Mitomycin c also inactivated by the acidic urine. Administer the chemotherapy agent through the main port, clamp with hemostat and attach to drainage bag. The system thus closed. Unclamp the catheter after 120 min. Run 1 liter saline through the irrigant port over next 30-60 min.

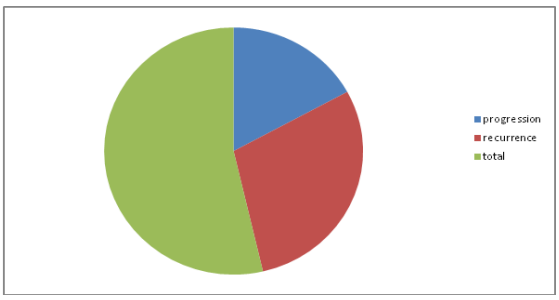
Remove and discard the Foley along with drainage bag. For BCG+MMC group 81 mg BCG infused once a week for 2 weeks, followed by 40 mg mitomycin in 40 ml normal saline or distilled water once a week for four weeks. For MMC group Mitomycin c 40mg in 40cc normal saline or distilled water,

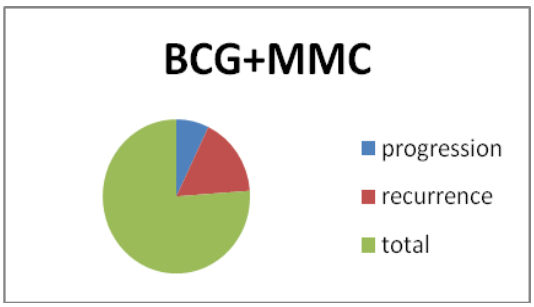
The procedure repeat weekly fro 6 weeks

Patient instructed to have fallow up cystoscope every 3 months for the 1st year, every 6 months for the next year then yearly. Average fallow up 36 months

Results

Of the 83 randomly assigned patients, the analysis demonstrated a highly significant difference in the recurrence rate. Patients assigned sequential BCG and Mitomycin c had lower recurrence rate 16.6 % (7 patients) versus 29.2% (12 patients) in those assigned for Mitomycin c alone, the difference between groups 12.6%; The progression rate in patients assigned sequential BCG and Mitomycin c about 7% (3 patients) versus 17% (7 patients) in those assigned for Mitomycin c alone, the difference between groups 10 %.





Progression rate and recurrence in MMC group Distribution according to recurrence rate in relation to stage and grade.

Therap. trial	TaG2		TaG3		T1G1		T1G2		T1G3	
	+ve	-ve	+ve	-ve	+ve	-ve	+ve	-ve	+ve	-ve
BCG+ Mitomy. group	0 0%	3 100 %	2 14.3 %	12 85.7%	1 10%	9 90%	1 12.5	7 87.5%	3 42.8%	4 57.2 %
Mitomy. group	1 25 %	3 75%	4 33.3 %	8 66.6%	1 11%	8 89%	2 25 %	6 75%	4 50%	4 50%
Total recur.	1 14 %	6 86%	6 23%	20 77%	2 11%	16 89%	3 19 %	13 81%	7 47%	8 53%

According to tumor stage and grade there is significant statistical difference between the number of cases of recurrence in the two different therapeutic trial (p value < 0.05).

Clinical Trial	TaG2		TaG3		T1G1		T1G2		T1G3	
	+ve	-ve	+ve	-ve	+ve	-ve	+ve	-ve	+ve	-ve
BCG+ mitomy. group	0 0%	3 100%	1 7%	13 93%	0 0%	10 100%	1 12.5 %	7 87.5 %	1 14%	6 86%
Mitomy. group	1 25 %	3 75%	2 17%	10 83%	1 11%	8 89%	1 12.5 %	7 87.5 %	2 25%	6 75%
Total progress.	1 14 %	6 86%	3 12%	23 88%	1 5%	18 95%	2 13%	14 87%	3 20%	12 80%

Distribution of cases according to progression rate in relation to stage and grade of tumor. According to tumor stage and grade there is significant statistical difference between the number of cases of progression in the two different therapeutic trial (p value < 0.05). We also notice that 68 % of patients with total recurrence and 60% of total progression are from grade 3. Distribution of cases according to recurrence rate in relation to tumor multiplicity.

Therapeutic trial	Single		Multiple	
	+ve	-ve	+ve	-ve
BCG+ Mitomcin group	1 3%	33 97%	6 75%	2 25%
Mitomycin Group	3 9%	29 91%	9 100%	0 0%
Total	4 6%	62 94%	15 88%	2 12%

According to tumor pattern and multiplicity there is significant statistical difference between recurrence rate in the two different therapeutic trial (p value <0.05), 78.9% of patients with recurrence are from the patients with multiple tumor and about 73.5 % of those with recurrence are from tumor with size larger than 3 cm. Distribution of cases according to progression rate in relation to tumor multiplicity.

Clinical trial	Single		Multiple	
	+ve	-ve	+ve	-ve
BCG+ Mitomcin group	0 0%	34 100%	3 37.5%	5 62.5%
Mitomycin Group	2 6%	30 94%	5 55.5%	4 44.5%
Total	2 3%	64 97%	8 47%%	9 53%

According to tumor pattern and multiplicity there is significant statistical difference between progression rate in the two different therapeutic trial (p value <0.05). Distribution of cases according to recurrence rate in relation to tumor size

Therapeutic trial	<3cm		>3cm	
	+ve	-ve	+ve	-ve
BCG + mitomycin group	2 12.5%	14 87.5%	7 27%	19 73%
Mitomycin Group	5 33%	10 67%	7 27%	19 73%
Total	7 22.5%	24 77.5%	14 27%	38 73%

According to tumor size or volume there is significant statistical difference between recurrence rate in the two different theraputic trial (p value <0.05). Distribution of cases according to progression rate in relation to tumor size.

Therapeutic trial	<3cm		>3cm	
	+ve	-ve	+ve	-ve
BCG + mitomycin group	1 6%	15 94%	2 8%	24 92%
Mitomycin Group	3 20%	12 80%	4 15%	22 85%
Total	4 13%	27 87%	6 11.5%	46 88.5%

According to tumor size or volume there is significant statistical difference between progression rate in the two different theraputic trial (p value <0.05). However the side-effects were mainly localized to the bladder, the complications after the treatment more common in patients receive sequential BCG and mitomycin c than in those receive mitomycin c alone. Cystitis occur in about 83% of patients receiving sequential BCG and mitomycin c, and about 4% developed fever and chills. While in patients receive mitomycin alone the complications are less cystitis in 10%, rash in about 6% and myelosuppression 5%.

Therapeutic trial	Cystitis	Myelosuppression	Fever & chills	Rash
BCG+MMC	35 (83)	0	2 (4.7%)	0%
MMC	4 (10%)	2 (5%)	0	3 (7%)

Discussion

It is well known from the literature that malignant cells are more sensitive to sequential immunotherapy and chemo-therapy versus chemotherapy alone. This probably because the BCG-induced inflammation might increase the permeability of the bladder mucosa such that mitomycin c can reach the target tissue more easily and exert its anticancer effect.

Superficial bladder tumors, due to their endocavitary location, have represented a model for the administration of local immunotherapy and chemotherapy for a long time. The present study investigated the efficacy and safety of sequential immunotherapy followed by chemotherapy regimen compared to intravesical chemotherapy alone as adjuvant treatment for superficial bladder cancer after a complete transurethral resection. Local side effects, in the form of cystitis symptoms and suprapubic pain, were more severe in patients who underwent sequential BCG with mitomycin c. However, local side effects did not influence the completion of the treatment and were transitory, asymptomatic, and self-recovering shortly after the end of therapy. We thus report a higher incidence of side effects in the combined treatment group, although they were almost uniformly moderate and transient. These results are preliminary and need to be confirmed by larger prospective, multicentric studies. The combined treatment (BCG + MMC) was slightly more expensive than the routine instillation of chemotherapeutic agents alone. There is no consensus on the mitomycin c dose a 20 mg of MMC for 1 hour may be suboptimal. However, a MEDLINE search combining the keywords "MMC" and "bladder instillation" showed a total of 120 articles, 40 of which were particularly relevant and gave sufficient details. Although few articles mention 60 mg of MMC as a possible dose for prophylactic treatment, no results are given for this dose, and a warning is given that higher doses can increase the incidence and severity of side effects[49].

Looking only at published results, of the 40 studies, 16 studies (40%) used the 20 mg dose, eight studies (20%) used the 30 mg dose, and 16 studies (40%) used the 40 mg dose. According to the manufacture's labeling, the recommended dose is 40 mg for intravesical instillation, and the European Urological Association guidelines recommend 20 to 40 mg as the standard dose of MMC. Therefore, 40 mg is a widely accepted dose, recommended within a range of standard doses by many authorities so in our study, a dosage concentration of MMC 40 mg in 40 mL.

Au et al addressed the issue of adequate drug delivery to enhance the prophylactic efficacy of MMC. They compared the efficacy of an optimized 40 mg MMC dose regimen with that of a standard regimen commonly used in their community (20 mg). They introduced different variables, such as minimizing residual urine, reducing urine production during the instillation period, and alkalinizing the urine, so that the significance of the dose factor cannot be singled out, because of the many additional factors[50].

To confirm these clinical findings, we also conducted a clinical trial designed to assess the absorption rate of MMC following BCG instillation because the inflammatory reaction enhanced by BCG instillation probably increase the absorption of mitomycin c. According to this study, a dosage concentration of MMC 40 mg in 40 mL remained strongly below the accepted threshold for MMC-induced side effects.

We note that series displaying a lower recurrence rate usually have a different selection of patients, including those with good-risk cases, whereas in our study, we try to divide the patients equally between the two therapeutic trial with respect to tumor grade, stage, multiplicity and size of the tumor.

In conclusion

In our series, sequential BCG and mitomycin c appears to be more effective than mitomycin c alone in the treatment for superficial bladder tumors at 36-month follow-up, despite an increased but acceptable local toxicity. This probably because the BCG-induced inflammation might increase the permeability of the bladder mucosa such that mitomycin c can reach the target tissue more easily and exert its anticancer.

References

1. Nilsson S, Ragnhammar P, Glimelius B, et al: A systematic overview of chemotherapy effects in urothelial bladder cancer. Acta Oncol 40:371–390, 2001.
2. Oosterlinck W, Lobel B, Jakse G, et al: Guidelines on bladder cancer: The commonly advocated doses for mitomycin C are 2–40 mgEuropean Association of Urology Guidelines. Arhem, the Netherlands, EAU Healthcare Office, 2001, p 9.
3. Sakamoto N, Naito S, Kumazawa J, et al: Prophylactic intravesical instillation of mitomycin C and cytosine arabinoside for prevention of recurrent bladder tumor following surgery for upper urinary tract tumors: A prospective randomised study. Int J Urol 8:212–216, 2001.
4. Au JL, Badalament RA, Wientjes MG, et al: Methods to improve efficacy of intravesical mitomycin C: Results of a randomized phase III trial. J Natl Cancer Inst 93:597–604, 2001.
5. Paroni R, Salonia A, Lev A, et al: Effect of local hyperthermia of the bladder on mytomicin C pharmacokinetics during intravesical chemotherapy for the treatment of superficial transitional cell carcinoma. Br J Pharmacol 52:273–278, 2001.
6. Parkin DM. The global burden of urinary bladder cancer. Scand J Urol Nephrol Suppl 2008;218:12-20.
7. 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.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. Bohle A, Jocham D, Bock PR. Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: A formal meta-analysis of comparative studies on recurrence and toxicity. J Urol 2003;169:90-5.
14. Han RF, Pan JG. Can intravesical bacillus Calmette-Guerin reduce recurrence in patients with superficial bladder cancer? A meta-analysis of randomized trials. Urology 2006;67:1216-23.

15. Malmstrom PU, Sylvester RJ. An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guerin for non-muscle-invasive bladder cancer. Eur Urol 2009;56:247-56.
16. Brandau S, Suttmann H. Thirty years of BCG immunotherapy for non-muscle invasive bladder cancer: A success story with room for improvement. Biomed Pharmacother 2007;61:299-305.
17. Zlotta AR, van Vooren JP, Huygen K, Drowart A, Decock M, Pirson M, et al. What is the optimal regimen for BCG intravesical therapy? Are six weekly instillations necessary? Eur Urol 2000;37:470-7.
18. 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.
19. Sylvester RJ, van der MA, Lamm DL. Intravesical bacillus Calmette-Guerin 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;168:1964-70.
20. Martínez-Piñeiro JA, Martínez-Piñeiro L, Solsona E, Rodríguez RH, Gómez JM, Martín MG, et al. Has a 3-fold decreased dose of bacillus Calmette-Guerin the same efficacy against recurrences and progression of T1G3 and Tis bladder tumors than the standard dose? Results of a prospective randomized trial. J Urol 2005;174:1242-7.
21. Andius P, Fehrling M, Holmang S. Intravesical bacillus Calmette-Guerin therapy: Experience with a reduced dwell-time in patients with pronounced side-effects. BJU Int 2005;96:1290-3 .
22. Koya MP, Simon MA, Soloway MS. Complications of intravesical therapy for urothelial cancer of the bladder. J Urol 2006;175:2004-10.
23. Patard JJ, Rodriguez A, Leray E, Rioux-Leclercq N, Guille F, Lobel B. Intravesical Bacillus Calmette-Guerin treatment improves patient survival in T1G3 bladder tumours. Eur Urol 2002;41:635-41.
24. Shahin O, Thalmann GN, Rentsch C, Mazzucchelli L, Studer UE. A retrospective analysis of 153 patients treated with or without intravesical bacillus Calmette-Guerin for primary stage T1 grade 3 bladder cancer: Recurrence, progression and survival. J Urol 2003;169:96-100.
25. Hall MC, Chang SS, Dalbagni G, Pruthi RS, Seigne JD, Skinner EC, et al. Guideline for the management of nonmuscle invasive bladder cancer (stages Ta, T1, and Tis): 2007 update. J Urol 2007;178:2314-30.
26. Gontero P, Bohle A, Malmstrom PU, O'Donnell MA, Oderda M, Sylvester R, et al. The role of bacillus Calmette-Guerin in the treatment of non-muscle-invasive bladder cancer. Eur Urol 2010;57:410-29.
27. Gasion JP, Cruz JF. Improving efficacy of intravesical chemotherapy. Eur Urol 2006;50:225-30.
28. Sternberg CN, Donat SM, Bellmunt J, Millikan RE, Stadler W, De Mulder P, et al. Chemotherapy for bladder cancer: Treatment guidelines for neoadjuvant chemotherapy, bladder preservation, adjuvant chemotherapy, and metastatic cancer. Urology 2007;69:62-79.
29. Nieder AM, Brausi M, Lamm D, O'Donnell M, Tomita K, Woo H, et al. Management of stage T1 tumors of the bladder: International Consensus Panel. Urology 2005;66:108-25.
30. Oosterlinck W, Solsona E, Akaza H, Busch C, Goebell PJ, Malmström PU, et al. Low-grade Ta (noninvasive) urothelial carcinoma of the bladder. Urology 2005;66:75-89.
31. Sylvester RJ, van der Meijden AP, Witjes JA, Kurth K. Bacillus calmette-guerin versus chemotherapy for the intravesical treatment of patients with carcinoma in situ of the bladder: A meta-analysis of the published results of randomized clinical trials. J Urol 2005;174:86-91.
32. Kaasinen E, Rintala E, Hellström P, Viitanen J, Juusela H, Rajala P, et al. Factors explaining recurrence in patients undergoing chemoimmunotherapy regimens for frequently recurring superficial bladder carcinoma. Eur Urol 2002;42:167-74.
33. Witjes JA, Hendricksen K. Intravesical pharmacotherapy for non-muscle-invasive bladder cancer: A critical analysis of currently available drugs, treatment schedules, and long-term results. Eur Urol 2008;53:45-52.
34. Bartoletti R, Cai T, Gacci M, Giubilei G, Viggiani F, Santelli G, et al. Intravesical gemcitabine therapy for superficial transitional cell carcinoma: Results of a Phase II prospective multicenter study. Urology 2005;66:726-31.
35. Huncharek M, Kupelnick 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.
36. 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.
37. 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.
38. Liu B, Zhang Y, Wang Z, Ding Q, Chen B, Wang J, et al. Single instillation of epirubicin for the prophylaxis of recurrent primary superficial bladder carcinoma. Zhonghua Wai Ke Za Zhi 2002;40:112-5.
39. Rajala P, Kaasinen E, Raitanen M, Liukkonen T, Rintala E. Perioperative single dose instillation of epirubicin or interferon-alpha after transurethral resection for the prophylaxis of primary superficial bladder cancer recurrence: A prospective randomized multicenter study--FinnBladder III long-term results. J Urol 2002;168:981-5.
40. Torelli F, Catanzaro F, Conti G, Comeri CG, Risi O, Pino R, et al. High-dose epirubicin in the prophylactic treatment of T1G2 superficial bladder tumors. Eur Urol 2001;39:11-4.
41. Newling DW, Hetherington J, Sundaram SK, Robinson MR, Kisbenedek L. The use of valrubicin for the chemoresection of superficial bladder cancer: A marker lesion study. Eur Urol 2001;39:643-7.
42. Gontero 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.
43. 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.
44. 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.
45. Gontero P, Casetta G, Maso G, Sogni F, Pretti G, Zitella A, et al. Phase II study to investigate the ablative efficacy of intravesical administration of gemcitabine in intermediate-risk superficial bladder cancer (SBC). Eur Urol 2004;46:339-43.
46. Dalbagni G, Russo P, Bochner B, Ben-Porat L, Sheinfeld J, Sogani P, et al. Phase II trial of intravesical gemcitabine in bacille Calmette-Guerin-refractory transitional cell carcinoma of the bladder. J Clin Oncol 2006;24:2729-34.
47. 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.
48. Maffezzini M, Campodonico F, Canepa G, Capponi 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.
49. 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
50. 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.