Symposium

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 immunomodualtory 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).[1] 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.[2,3] 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.[4] 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.[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.

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.[8] In this risk assessment tool, risk factors are given

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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.

Table 1: Weighting used to calculate recurrence and progression scores[8,9]

Factor	Recurrence	Progression
Number of tumors		
Single	0	0
2-7	3	3
> 8	6	3
Tumor diameter		
< 3 cm	0	0
> 3 cm	3	3
Prior recurrence rate (recurrence/year)		
Primary	0	0
< 1	2	2
> 1	4	2
Category		
Ta	0	0
T1	1	4
Concomitant CIS		
No	0	0
Yes	1	6
Grade (1973 WHO)		
G1	0	0
G2	1	0
G3	2	5
Total score	0-17	0-23

CIS, carcinoma *in situ*.

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.[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 2: Probability of recurrence and progression according to total score[8,9]

Recurrence score	Probability of recurrence				Recurrence risk group
	At 1 Year		At 5 Years		
	Percentage	(95% CI)	Percentage	(95% CI)	
0	15	(10-19)	31	(24-37)	Low risk
1-4	24	(21-26)	46	(42-49)	Intermediate risk
5-9	38	(35-41)	62	(58-65)	
10-17	61	(55-67)	78	(73-84)	High risk
Progression score	**Probability of progression**				**Progression risk group**
	At 1 Year		At 5 Years		
	Percentage	(95% CI)	Percentage	(95% CI)	
0	0.2	(0-0.7)	0.8	(0-1.7)	Low risk
2-6	1	(0.4-1.6)	6	(5-8)	Intermediate risk
7-13	5	(4-7)	17	(14-20)	High risk
14-23	17	(10-24)	45	(35-55	

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 If fever >102 F or lasts >48 hr needs antitubercuolus therapy
	Hematuria	1-34% incidence 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
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 Mostly asymptomatic	If symptomatic INH with RFP for 3 months
	Granulomatous epididymoorchitis	Infrequent complication Local induration and pain	If fever or leucocytopenia 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 Systemic absorption associated with traumatic catheterization or bladder inflammation Fever, chills, hypotension and mental confusion. Can progress to multi-organ dysfunction	Emergency hospital admission and treatment, possible intensive care management. INH 300 mg daily RFP 600 mg daily 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% Patients on a maintenance schedule may be at higher risk	Treatment consists of withholding BCG and hydrodistention. 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 834 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.[11] 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,

Strategies to establish a perioperative plan for intravesical chemotherapy
- Meet with pharmacy and nursing personnel to discuss plans and verify the drug availability.
- Include immediate perioperative chemotherapy on the operative schedule to alert staff.
- Call pharmacy before or early into case to verify need for drug.
- Set up a closed system to minimize nursing contact with chemotherapeutic agent.[2]

Method of administration
- Place a 3-way catheter in the OR attached to an irrigant fluid, which is left turned off.
- Administer the chemotherapy agent through the main catheter port, clamp with hemostat and attach to a drainage bag .The system is thus closed.
- Staff should be notified to unclamp after 1 hour.
- Run 1 liter of saline through the irrigant port over next 30–60 minutes,
- Remove and discard the Foley along with urinary drainage bag into biohazard container.[2]

Table 4: Practical aspects of intravesical chemotherapy

Table 5: Complications of intravesical chemotherapy

Complication	Association	Suggested treatment
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	Oxybutynin, phenazopyridine, or propantheline bromide.
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.

95% CI 0.38 to 0.84, $P = 0.005$). In the subgroup treated with BCG maintenance all six individual studies showed a significant superiority of BCG over mitomycin C (OR 0.43, 95% CI 0.35 to 0.53, $P < 0.001$). Results suggest superiority of BCG over mitomycin C for 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 Malmstorm *et al*, analyzed nine trials that included 2820 patients were identified.[13] 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,[11,17] while others did not.[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.[23]

In summary a recent literature review by Gontero *et al*,[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.[25] Among the subtypes, interferon-α has been the most extensively studied. Its efficacy is dose dependent.[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.[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.[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.[32] The absorption and effectiveness of the drug is determined by physiochemical properties of the drug, physiological variables in urine and tissue pharmacokinetics.[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.[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.[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.[5,9,23,36,37] The EORTC meta-analysis found no significant differences in efficacy among the chemotherapeutic agents studied. Therefore, choice of agent is left to the physician.[38]

The time period within which the installation is completed is very important. In all the studies included in the EORTC meta-analysis, the instillation was administered within 24 h.[16] Kaasinen *et al*, reported that the risk of recurrence is twice when the instillation was not given within 24 h of TURBT.[39] However, an immediate, single instillation of chemotherapy should be avoided when intra- or extraperitoneal perforation of the bladder is suspected.[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.[9,23,36,37] 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.[40] Review of controlled trials showed a mean decrease in tumor recurrence by 14%.[41] 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.[42] 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.[43] The authors suggested that use of long-term instillations for 1 year should only be considered when an immediate instillation has not been performed.[43]

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.[44]

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.[40] Lamm *et al*, performed a meta-analysis of five controlled trials and reported that the recurrence rate was reduced by 15%.[45] The advantage of MMC was 15% (52% recurrences in the control groups versus 37% in the MMC group).[45] A long-term effect on recurrence and disease progression was not demonstrated.[45] 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%.[46] The 6 and 9 weekly instillation when compared with 6 weekly BCG-RIVM had similar disease-free percentage for pTa , pT1 and CIS.[47,48] 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%).[49] 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.[50]

Huland *et al*,[51] 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.[53]

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.[54] 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%.[55]

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.[9,23]

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%.[46,56] The most frequent side effect of ADM is chemical cystitis, seen in 25-30% of the patients.[57] Rare side effects are allergic reactions (0.3%), gastrointestinal side effects (1.7%) and fever (0.8%).

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 showed 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

Eoquin (EO9) (Spectrum Pharmaceuticals Inc., Irvine, CA) is a novel indolequinone derivative of MMC. The enzyme deoxythmidine- diaphorase which is found in 40% of bladder tumors activates EO9. The normal bladder tissue lacks this enzyme and hence does not activate E09 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.

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