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Intravesical Gemcitabine in Recurrent Superficial Bladder Carcinoma: Preliminary Results on Ablative Efficacy and Tolerability

FABIO CAMPODONICO, GIORGIO CANEPA, GIACOMO CAPPONI, LUIGI BOZZO and MASSIMO MAFFEZZINI

Department of Urology, Galliera Hospital, 14 Mura delle Cappuccine, 16128 Genoa, Italy

Abstract. *Background: The ablative potential and toxicity of gemcitabine, administered intravesically in low stage and grade superficial transitional cell carcinoma (TCC), were evaluated. Patients and Methods: Patients with a history of recurrent Ta-T1, G1-G2 bladder TCC were considered eligible for the study. Gemcitabine was administered intravesically at 40 mg/mL concentration (2000 mg in 50 ml saline) in one weekly instillation for 4 consecutive weeks. Fifteen days after the last instillation, patients were submitted to transurethral resection (TUR). Results: Twenty-six patients were evaluable for toxicity, and 20 were evaluable for response, 6 patients being excluded due to toxicity. A complete response was achieved by 10 out of 20 patients (50%), whereas no response was documented in the remainder. Toxicity leading to treatment interruption was grade 3 in 1 patient and grade 2 in 5 patients. Conclusion: Intravesical gemcitabine administered at 40 mg/mL showed the capability of ablating small volume, superficial TCC in 50% of the population under study, with acceptable tolerability.*

Transitional cell carcinoma (TCC) is the most common tumor of the bladder and, at initial diagnosis, it occurs as a superficial disease in approximately two-thirds of patients. The tumor is histologically limited to the transitional epithelium, lamina propria and/or muscularis mucosae. The natural history of superficial TCC shows a high rate of recurrence, around 80%, and a lower rate of stage-grade progression (10% to 20%). Transurethral resection of bladder tumor(s), or TURBT, is considered the treatment of choice. However, it is commonly followed by intravesical instillation of antitumoral or immunomodulating agents with the purpose of reducing the incidence of recurrence and progression of the disease (1). Immunotherapy with bacillus Calmette-Guérin (BCG) is presently the most effective agent, but it can be associated with adverse effects ranging from mild dysuria to systemic tuberculosis (2). Several chemotherapeutic drugs, including thiotepa, doxorubicin, mitomycin C, mitoxantron, epirubicin and valrubicin, have been used for prophylaxis of recurrences after TURBT. Their range of efficacy, evaluated by using ablative doses, is 40% to 60% on average, but the recurrence rate (number of tumor recurrences divided by the total duration of follow-up for all treated patients) is far lower than BCG therapy (3-7). New chemotherapeutic agents are advisable to enhance anticancer activity and prophylactic efficacy and to influence the long-term outcome of superficial bladder cancer. Gemcitabine is a pyrimidine analog that conferred a similar survival advantage, with a better safety profile, than the conventional chemotherapy combination (MVAC) in locally advanced and metastatic bladder cancer (8). Recently, gemcitabine was also used in association with others agents, such as epi-doxorubicin, oxaliplatin and paclitaxel, with the aim of investigating a potential synergic activity in urothelial cancer (9-11). The proven efficacy of systemical therapy against advanced bladder cancer led urologists to consider gemcitabine as a potential new agent for the treatment of superficial TCC, by intravesical administration. Phase I parmacokinetic studies showed a very low concentration of the metabolite difluorodeoxyuridine in the systemic circulation, indicating minimal absorption through the bladder wall (12-14). Moreover, experimental studies in dogs documented that gemcitabine can be safely given at intravesical doses of 1000 mg/m^2 (15). We tested the ablative potential of up-front endovesical chemotherapy in previous studies with different drugs, and we present, here,

Correspondence to: Fabio Campodonico, MD, Department of Urology, Galliera Hospital, 14 Mura delle Cappuccine, 16128 Genoa, Italy. Tel: + 39 010 5634863, Fax: + 39 010 5634866, e-mail: fabio.campodonico@galliera.it

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Table I. *Toxicity according to the Common Toxicity Criteria version 3.0.*

Toxicity	Grade I	Grade II	Grade III
Hematological			
Leukocytes	1	1	1
Transaminases	1	(2)	
Lipase	1		
Amylase	1		
Urogenital			
Dysuria	7	(1)	
Urgency	3		
Gastrointestinal			
Nausea	4		
Vomiting	2		
Abdominal pain		2	
Dermatological			
Chemical dermatitis	2		
Others			
Fatigue	1		

Table II. *Tumor characteristics and treatment response.*

Previous histology	Tumors		Previous treatment	Response
	No.	cm		
TaG1	2	1	-	CR
TaG1	1	0.5	-	CR
TaG1	1	1	-	NR(TaG1)
TaG1	1	1	-	CR
TaG1	1	1	-	NR(TaG1)
TaG1	1	0.5	-	CR
TaG1	2	1.5	-	CR
TaG1	2	1	MC + BCG	CR
TaG1	1	0.5	EPI	NR(TaG1)
TaG1	3	1.5	-	CR
TaG1	2	1	-	NR(TaG1)
T1G1	2	1.5	EPI	NR(T1G1)
TaG2	2	1.5	EPI	NR(TaG2)
TaG2	1	1	-	CR
T1G2	4	1.5	MC + BCG	CR
T1G2	3	1	-	NR(TaG1)
T1G2	1	0.5	MC	NR(TaG1)
T1G2	1	0.5	-	NR(TaG1)
T1G2	1	0.5	-	CR
T1G2	1	1.5	-	NR(T1G2)

EPI (Epirubicin); MC (Mitomycin C); BCG (bacillus Calmette-Guérin)

a study with intravesical gemcitabine in low grade Ta-T1 recurrent superficial bladder cancer.

Patients and Methods

Patient selection. Patients with a history of recurrent Ta-T1, G1-G2 bladder TCC were considered eligible. Inclusion criteria were: age >18 years, informed consent, performance status WHO 0-2, normal upper urinary tract at IVP. Patients with a diagnosis of G3 tumor and/or Cis were excluded from the study. The pre-study clinical evaluation comprised medical history, general examination and blood count, including liver and kidney function. The features of bladder cancer were: single or multiple papillary tumors, no more than three lesions, and with a maximum diameter no more than 1.5 cm. Previous intravesical treatment with chemo-immunoprophylactic agents was admitted if given at least 6 months before patient recruitment. The study protocol was approved by the local Ethics Committee.

Treatment schedule and response criteria. Gemcitabine (Gemzar®, Eli Lilly) was prepared in solution as suggested by phase I studies. Two thousand mg of drug were diluted in 50 ml normal saline solution to achieve the saturation dose of 40 mg/mL. One weekly intravesical instillation for 4 consecutive weeks was the established protocol. Patients were invited to retain the solution in the bladder for at least for 1 hour before micturition. Complete blood count and blood chemistry were assessed 2 days before and 2 days after each instillation. Two weeks following the last instillation, a mapping of the bladder mucosa and resection of tumor site(s) were obtained in the patients who had a complete response, whereas any residual lesion was resected in those who did not respond. A complete response to treatment (CR) was defined by a complete disappearance of the tumor and negative histology. The presence of any residual lesion was considered as no response (NR). Therefore, the category of partial response was not considered.

Systemic and local toxicity. Toxicity was assessed using the Common Toxicity Criteria v 3.0 (16). Grade 3 side-effects determined patient exclusion from the study. In case of grade 2 toxicity, the treatment was delayed for 1 week and repeated; if toxicity relapsed at grade 2, the treatment was stopped. Side-effects were checked after each instillation and recorded on the data base. The blood count and chemistry were routinely performed twice a week, before and after each drug instillation. Adverse effects of uncommon presentation were also documented by photograph (*i.e.* skin reaction).

Results

From July 2003 to June 2004, 27 patients were enrolled. The group was composed of nineteen males and eight females, with a median age of 69 years (range 44-82). One male patient was excluded because of stenosis of the anterior urethra. Among the patients, twenty concluded the 4 weekly instillations, while six patients experienced adverse effects that did not allow them to complete the protocol. Thus, twenty-six patients were evaluable for side-effects, as displayed in Table I, and twenty patients for drug ablative activity. The drug was retained in the bladder for less than 1 hour in 32 out of 94 intravesical instillations performed, 1 hour or more in 34, and 1 and a half hours in 28 instillations.

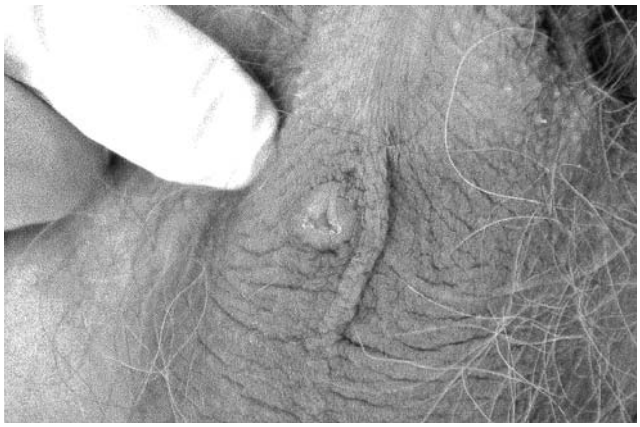

Figure 1. *Chemical dermatitis appearing as a scrotal ulcer 3 days after gemcitabine instillation.*

Ablative efficacy. The tumor features of the twenty histologically evaluable patients are depicted in Table II. The population under study was composed of patients with recurrent tumors which were at stage Ta (thirteen patients) and T1 (seven), at the last TUR. The grade of the disease was G1 in twelve, and G2 in eight patients. According to our study protocol, after the fourth instillation the patients were submitted to TURB. The ablative efficacy was complete in ten patients out of twenty. Among the non responders, no patient had progression in stage or grade, or increase in size and number of bladder tumors. The first control cystoscopy at 3 months post TUR showed no recurrence in eight patients, and a single bladder recurrence in one patient. Another patient had negative cystoscopy, but positive urine cytology and fluorescence *in situ* hybridization (FISH).

Systemic and local toxicity. The most severe systemic side-effect was a grade 3 leukopenia occurring at the first instillation, with the drug retained for 1 hour in the bladder. Hematological toxicity also included one patient with grade 2 absolute neutropenia, and another patient with a grade 1 lymphopenia. Blood chemistry showed a grade 1 amylase and lipase associated with a pancreatitis-like syndrome. Furthermore, in two patients, a grade 2 elevation of transaminases was observed. One patient was under antibiotic medication for prophylaxis of endocarditis, and the second patient had a misdiagnosed HCV chronic hepatitis. Abdominal pain, in the epigastric area, was always associated with nausea and vomiting in another two patients. The commonest local side-effect was a transient and mild dysuria, with or without urgency. In one female patient, a grade 2 dysuria was probably related to a severe pre-existent chronic genital mycosis, which worsened during treatment. An unusual side-effect was chemical dermatitis of the scrotal skin, following the direct contact of gemcitabine due to urine dripping after micturition, in patients with prostatic hyperplasia. The wounds resembled painful burns, easily bleeding, of 2 and 5 cm diameter. Spontaneous healing was achieved in 10-14 days without scar formation (Figure 1). All side-effects, according to the Common Toxicity Criteria, are shown in Table I.

Discussion

The first reported phase I study on intravesical gemcitabine was performed by Dalbagni *et al.* in patients with BCG-refractory high-risk TCC of the bladder (17). Eighteen patients were treated by using a drug dose-escalation to achieve the maximal concentration of 20 mg/mL in six patients. The dose was given for 1 hour twice a week for 3 weeks, and after a 1-week break, a new course of 6 instillations for 3 weeks was done. Although the ablative efficacy was not the first endpoint of this study, a complete response was obtained in three patients out of six. A grade 3 hematological toxicity (neutropenia and thrombocytopenia) was observed in one patient. Moreover, among patients treated at a lower gemcitabine concentration (nine patients), the authors found two grade 3 urinary frequency, one grade 3 hand-foot syndrome, and five grade 2 hematuria. Considering the number of side-effects reported in relation to the doses, it is likely that reconstituting the drug in a buffered solution may play a role in terms of systemic absorption with the consequent toxicity. In fact, alkalinization of urine has been described as a factor enhancing the pharmacological activity and bladder absorption of intravesically-administered chemotherapeutic agents (18). Laufer *et al.* performed a dose finding and pharmacokinetic study in fifteen patients with recurrent superficial bladder cancer (13). Gemcitabine was intravesically given once a week for 6 consecutive weeks, and retained for 2 hours in the bladder. Four patients received a maximal dose-escalation of 40 mg/mL. The plasma level of gemcitabine in such patients was low and transient, and only one patient complained of a grade 2 dysuria. More recently, Witjes *et al.* reported a phase I study of 6 weekly instillations of gemcitabine, held in the bladder for 1 hour. In three patients treated at 40 mg/mL concentration, the plasma level of gemcitabine reached a very low peak between 30 and 60 minutes, and only grade 1 side-effects were observed (14). These studies showed the feasibility and safety of using the 40 mg/mL gemcitabine concentration, which should be the recommended dose in further clinical studies.

The first phase II study of gemcitabine used in a chemoablative protocol was reported by Tizzani *et al.* (19) Twenty patients with intermediate-risk superficial bladder carcinoma were enrolled in a marker lesion study (20). The drug was administered once a week for 6 weeks, starting seven days after TURBT and leaving a marker lesion. Only grade 1 side-effects were reported, without significant

changes in blood count and biochemistry. Among the sixteen patients evaluated after endoscopy and histology, ten patients displayed a complete response, and no case of disease progression was observed.

In our study, twenty patients concluded the protocol, and a complete response was achieved by ten patients. Of twenty-six evaluable patients, treated at maximal drug saturation dose of 40 mg/mL, only one grade 3 toxicity was recorded. In this patient, the blood failure occurred immediately after the first instillation, but recovery of the blood count was complete 7 days later. Therefore, we consider giving only one instillation a week to be a safe procedure. The grade 2 toxicity found concerned transaminases elevation and abdominal pain. The transaminases elevation occurred as a moderate progressive increase, which was noted after each intravesical instillation. However, the relationship with treatment is only to be considered as "possibly related", because one patient was on antibiotic medication, and the other one had a misdiagnosed hepatitis C. Abdominal pain occurred without prodromes.

In conclusion, with strict criteria of response (*i.e.* no partial response was contemplated), and only 4 weekly instillations, gemcitabine administered intravesically at a dose of 40 mg/mL showed the capability of ablating low stage and grade TCC of the bladder in 50% of the population under study. Toxicity was acceptable in the majority of cases, however, it led to treatment interruption in six patients. The ablative potential could be more precisely defined by further studies comparing gemcitabine to already known drugs.

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References

1 Maffezzini M, Audisio R, Pavone-Macaluso M and Hall RR: Bladder cancer. Crit Rev Oncol Hematol *27*: 151-153, 1998.

2 Lamm DL, Van der Meijden PM, Morales A *et al*: Incidence and treatment of complication of bacillus Calmette-Guérin intravesical therapy in superficial bladder cancer. J Urol *147*: 596-600, 1992.

3 Zincke H, Benson RC, Hilton JF *et al*: Intravesical thiotepa and mitomycin C treatment immediately after transurethral resection and later for superficial (stages Ta and Tis) bladder cancer: a prospective, randomized, stratified study with crossover design. J Urol *134*: 1110-1114, 1985.

4 Lamm DL, Blumenstein BA, Crawford ED *et al*: A randomized trial intravesical doxorubicin and immunotherapy with bacillus Calmette-Guérin for transitional-cell carcinoma of the bladder. N Engl J Med *325*: 1205-1209, 1991.

5 Oosterlink W, Kurth KH, Schroder F *et al*: A prospective European Organization for Research and Treatment of Cancer Genitourinary Group randomized trial comparing transurethral resection followed by a single intravesical instillation of epirubicin or water in single stage Ta, T1 papillary carcinoma of the bladder. J Urol *149*: 749-752, 1993.

6 Maffezzini M, Simonato A, Zanon M, Raber M and Carmignani G: Up-front intravesical chemotherapy for low stage, low grade recurrent bladder cancer. J Urol *155*: 91-93, 1996.

7 Steinberg G, Bahnson R, Brosman S *et al*: Efficacy and safety of valrubicin for the treatment of bacillus Calmette-Guérin refractory carcinoma *in situ* of the bladder. The Valrubicin Study Group. J Urol *163*: 761-767, 2000.

8 Von der Maase H, Hansen SW, Roberts JT *et al*: Gemcitabine and cisplatin *versus* methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol *18*: 3068-3077, 2000.

9 Neri B, Doni L, Fulignati C, Gemelli MT *et al*: Gemcitabine *plus* epi-doxorubicin as first-line chemotherapy for bladder cancer in advanced or metastatic stage: a phase II. Anticancer Res *22*: 2981-2984, 2002.

10 Culine S, Rebillard X, Iborra F *et al*: Gemcitabine and oxaliplatin in advanced transitional cell carcinoma of the urothelium : a pilot study. Anticancer Res *23*: 1903-1906, 2003.

11 Perabo FG, Lindner H, Schmidt D *et al*: Preclinical evaluation of gemcitabine/paclitaxel-interactions in human bladder cancer lines. Anticancer Res *23*: 4805-4814, 2003.

12 Abbruzzese JL, Grunewald R and Weeks EA: A phase I clinical, plasma, and cellular pharmacology study of gemcitabine. J Clin Oncol *18*: 2780-2787, 2000.

13 Laufer M, Ramalingam S, Schoenberg MP *et al*: Intravesical gemcitabine therapy for superficial transitional cell carcinoma of the bladder: a phase I and pharmacokinetic study. J Clin Oncol *21*: 697-703, 2003.

14 Witjes JA, van der Heijden AG, Vriesema JL, Peters GJ, Laan A and Schalken JA: Intravesical gemcitabine: a phase I pharmacokinetic study. Eur Urol *45*: 182-186, 2004.

15 Cozzi PJ, Bajorin DF, Tong W, Nguyen H, Scott J, Heston WDW *et al*: Toxicology and pharmacokinetics of intravesical gemcitabine: a preclinical study in dogs. Clin Cancer Res *5*: 2629-2637, 1999.

16 http://ctep.cancer.gov

17 Dalbagni G, Russo P, Sheinfeld J *et al*: Phase I trial of intravesical gemcitabine in bacillus Calmette-Guérin-refractory transitional-cell-carcinoma of the bladder. J Clin Oncol *20*: 3193-3198, 2002.

18 Benet LZ, Kroetz DL and Sheiner LB: Pharmacokinetics: the dynamics of drug absorption, distribution and elimination. *In:* The Pharmacological Basis of Therapeutics (Hanehman JG and Limbird LE, eds). New York, McGraw-Hill pp. 4-5, 1996.

19 Tizzani A, Gontero P, Casetta G *et al*: Intravesical gemcitabine in the treatment of intermediate risk superficial transitional cell carcinoma (TCC) of the bladder: a marker lesion study. Eur Urol *1(Suppl 2)*: 218, 2003 [Abstract LB12].

20 Van der Meijden APM, Hall RR, Pavone Macaluso M, Pawinsky A, Sylvester R and Van Glabbeke M: Marker tumor reponse to the sequential combination of intravesical therapy with mitomycin C and BCG-RIVM in multiple superficial bladder tumors. Report from the European Organization for Research and Treatment on Cancer-Genitourinary Group (EORTC 30897). Eur Urol *29*: 199-203, 1996.

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