Original Paper

Urologia Internationalis

Urol Int 2006;76:106–111
DOI: 10.1159/000090870

Received: May 27, 2005
Accepted after revision: October 6, 2005

Intravesical Gemcitabine in BCG-Refractory T1G3 Transitional Cell Carcinoma of the Bladder: A Pilot Study

Mauro Gacci[a] Riccardo Bartoletti[a] Tommaso Cai[a] Stefano Nerozzi[b] Novello Pinzi[c] Fabrizio Repetti[c] Fabrizio Viggiani[d] Paolo Ghezzi[e] Gabriella Nesi[f] Marco Carini[a] and TUR (Toscana Urologia) Group

Departments of Urology, [a]University of Florence, Florence; [b]Hospital of Pistoia, Pistoia; [c]Hospital of Lucca, Lucca; [d]Hospital of Grosseto, Grosseto; [e]Department of Oncology, Hospital of Arezzo, Arezzo, and [f]Department of Human Pathology and Oncology, University of Florence, Florence, Italy

Key Words
Gemcitabine · Bacille Calmette-Guérin · Bladder tumor · Transitional cell carcinoma

Abstract
Objective: The aim of this pilot study is to analyze the safety and short-term efficacy of gemcitabine (GEM) as salvage intravesical therapy in a very selected population of bacille Calmette-Guérin (BCG)-resistant T1G3 patients. ***Methods:*** 9 recurrent BCG-refractory pT1G3 patients, unsuitable for radical treatment, were treated with GEM, and compared with 10 pT1G3 patients previously treated with at least two courses of transurethral resection plus BGC, with further conservative endovesical BCG administration. ***Results:*** Both intravesical administrations of GEM and BCG were generally well tolerated: no severe adverse events were reported. Of the 9 patients treated with GEM, 3 were recurrence-free after 13, 17 and 21 months and 7 kept an intact bladder, with an overall survival rate of 9 of 9. Among 10 patients treated with BCG instillation, 1 was recurrence-free after 27 months and 6 kept their bladders, with a survival rate of 8 of 10. ***Conclusions:*** Our experience confirms the high risk of tumor recurrence and progression of BCG-refractory pT1G3 transitional cell carcinoma. In this case, further BCG courses seem to be unsuitable, resulting in a high risk of tumor progression and mortality. The use of GEM in BCG-refractory pT1G3 patients has to be considered experimental until multicentric randomized studies with adequate follow-up are able to confirm the preliminary results of this pilot study.

Introduction

Grade-3 transitional cell carcinomas (TCCs) involving the lamina propria (pT1) are improperly classified as superficial bladder tumors. So-called T1G3 patients have 10 times the chance of muscle invasion and death from superficial bladder cancer than patients with other Ta–T1 tumors [1]. Therefore, the indication for immediate or deferred cystectomy for T1G3 bladder cancer treatment is still under discussion [2]. However, there is a great deal of evidence that some pT1G3 TCCs of the bladder will not progress; hence, immediate radical cystectomy for these cases should be considered during treatment [3].

The efficacy of bacille Calmette-Guérin (BCG) adjuvant treatment for conservative T1G3 tumor manage-

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0042–1138/06/0762–0106$23.50/0

Accessible online at:
www.karger.com/uin

Dr. Mauro Gacci
Department of Urology, University of Florence
Via Masaccio 102
IT–50132 Florence (Italy)
Tel. +39 055 427 9209, Fax +39 055 437 7755, E-Mail maurogacci@yahoo.it

Table 1. Patients and tumor characteristics, pathological data and follow-up of the GEM group

Patient No.	Age years	Sex	Recurrence	Last recurrence	Time from last recurrence months	Lesions	Tumor diameter cm	Adverse event	Recurrence after GEM	Progression after GEM	Time to recurrence/ progression months	Status	Follow-up months
1G	75	M	1	pTaG1	7	2	1	No	No	–	–	Vned	13
2G	68	M	1	pTaG2	9	2	4	No	–	pT2bG3[a]	13	Vned	18
3G	73	M	2 or >2	pTaG2	7	2	2	No	No	–	–	Vned	17
4G	74	M	2 or >2	pTaG3	9	2	1	No	pTaG2	–	6	Vned	19
5G	79	F	1	pT1G2	8	1	1	Irritative	pT1G2	–	8, 18	Vned	20
6G	82	M	2 or >2	pT1G3	6	3	1	No	pTaG2	–	5, 11, 19	Vned	20
7G	75	M	2 or >2	pT1G3	3	4	1	No	pT1G2	–	7	Vned	21
8G	87	F	1	pT1G3	3	3	1	No	–	pT2G3[b]	4, 17	Vned	17
9G	62	M	1	pT1G3	18	1	2	Fever	No	–	–	Vned	21

Vned = Alive with no evidence of disease.
[a] Radical cystectomy with orthotopic neobladder.
[b] Radical cystectomy with urethrocystoscopy.

ment has been described in many clinical trials [4, 5]; nevertheless, BCG may reduce local recurrences but not progression [6]. Although many trials have documented a 30–40% decrease in tumor recurrence after BCG, the endovesical administration of this drug is associated with local toxicity such as dysuria, and frequency or urgency [7]. Moreover, there is no effective treatment for further conservative management of pT1G3 patients with recurrence after BCG failure. Even though severe types of cytotoxic treatment, such as mitomycin C [8], epirubicin [9] or valrubicin [10], have been evaluated for BCG-resistant bladder tumors, effective and well-tolerated treatment is still missing.

Gemcitabine (GEM) is a pyrimidine analogue that has been shown to have strong anti-tumor activity in several solid neoplasms, such as pancreas and lung cancer [11, 12]. Moreover, GEM has been shown to be well tolerated and highly effective when administered systemically for the treatment of metastatic TCC [13]. Nevertheless, an animal study of endovesical GEM administration has documented that low molecular weight and deep bladder wall penetration allow a good toxicological and pharmacokinetic profile [14].

The aim of this pilot study is to analyze the safety and short-term efficacy of salvage intravesical chemotherapy with GEM in a selected population of BCG-refractory T1G3 patients unsuitable for cystectomy or refusing that option, through an observational comparative non-randomized trial.

Patients and Methods

T1G3 patients who did not respond to two 6-week courses of BCG (so-called 'BCG-refractory' [15]) were treated with endovesical GEM. The overall results were compared with a population of pT1G3 patients previously treated with at least two courses of transurethral resection (TUR) followed by BCG, with further conservative endovesical BCG administration. No patient was suitable for radical treatment owing to age (over 80 years) and anesthesiological risk (ASA 3), or personal refusal of cystectomy. Informed consent was obtained from all patients.

GEM Group

Nine patients with pT1G3 TCC were included in this group (table 1). Mean age was 74 ± 6 (range 62–80) years; 2 were female and 7 male. Two patients were over 80 years old with severe anesthesiological risk, while 7 refused radical cystectomy. Mean follow-up was 18.4 (13–21) months. The intravesical GEM regimen consisted of induction and maintenance courses with GEM (Gemzar®, Eli Lilly and Co, Indianapolis, Ind., USA). The induction course consisted of a 6-week administration of 2,000 mg of GEM diluted in 50 ml physiologic solution, placed inside the bladder with sterile catheterization and retained for at least 1 h. Maintenance therapy consisted of a single weekly instillation for 3 consecutive weeks at 3, 6, 12, 18 and 24 months.

BCG Group

Ten patients with pT1G3 TCC were included in this group (table 2). Mean age was 73.6 ± 11.9 (57–91) years; 2 were female and 8 male. Three patients were over 80 years old with severe anesthesiological risk, while 7 refused radical cystectomy. Mean follow-up was 19.9 (7–27) months. An intravesical BCG regimen was given, consisting of induction and maintenance courses with a low-dose Tice strain of BCG (OncoTICE®, Organon Italia S.p.A, Rome, Italy). The induction course consisted of a 6-week administration of 2 ml (5×10^8 CFU) of BCG Tice strain diluted in 50 ml of physiologic solu-

Table 2. Patients and tumor characteristics, pathological data and follow-up of the BCG group

Patient No.	Age years	Sex	Recurrence	Last recurrence	Time from last recurrence months	Lesions	Tumor diameter cm	Adverse event	Recurrence after BCG	Progression after BCG	Time to recurrence/ progression months	Status	Follow-up months
1B	67	M	2 or >2	pTaG2	7	1	2	No	pTaG2	–	8	Vned	23
2B	59	M	2 or >2	pTaG2	9	1	1	No	No	–	–	Vned	27
3B	75	M	1	pTaG2	6	5	2	Fever	–	pT4G3[a]	6, 13	Vned	21
4B	57	M	2 or >2	pTaG2	8	4	1	No	–	pT2G3[a]	8	Vned	21
5B	62	F	2 or >2	pTaG2	5	1	1	No	pTaG1	–	8, 13	Vned	27
6B	76	M	2 or >2	pTaG3	4	2	3	Hematuria	–	pT3bG3[b]	3	Dec.K	15
7B	86	M	2 or >2	pTaG3	6	2	1	No	pT1G1	–	3, 6	Vned	21
8B	91	F	2 or >2	pT1G1	7	1	3	No	pTaG2	–	11	Vned	7
9B	85	M	2 or >2	pT1G2	9	1	3	Fever	pTaG2	–	11	Vned	21
10B	78	M	2 or >2	pT1G3	7	2	1	No	–	pT2G3[c]	5	Dec.K	16

Vned = Alive with no evidence of disease; Dec.K = died of bladder tumor.
[a] Radical cystectomy with urethrocystoscopy.
[b] Radical cystectomy alone.
[c] Partial cystectomy with chemotherapy.

tion, placed inside the bladder with sterile catheterization and retained for at least 1 h. The maintenance therapy consisted of a single instillation per month at 3, 6, 12, 18 and 24 months.

TUR and Follow-Up

All patients underwent TUR of visible tumor with deep muscular tissue; additional samples were collected in suspected areas. The operation was performed under spinal anesthesia for most patients. At the end of the surgical procedure all macroscopic tumors were completely eradicated, and all specimens were evacuated and collected for pathology. Tumor size was defined as the largest tumor measure compared to the resection loop. Pathological evaluation was carried out by the same onco-uro-pathologists for all bladder tumors, according to the classification by Pagano et al. [16]. The catheter was removed 3–4 days after TUR and patients were discharged the day after catheter removal.

Patients with associated carcinoma in situ were not included in the study for several reasons: the proper attitude of this kind of tumor to progress; the complexity of monitoring flat lesions by cystoscopy; the lack of experience in the literature about GEM in carcinoma in situ, and moreover, Palou et al. [17] recently reported their experience with GEM in pTa–pT1 tumors, excluding carcinoma in situ.

A second TUR, 3 months after TUR of pT1G3 tumors, was not achieved, although these patients presented significant risk of staging error [18]; this procedure is usually carried out with the aim of switching from a conservative approach to a radical one if an invasive neoplasm is identified. However, these very selected patients were not suitable for radical cystectomy, therefore, we only achieved salvage endovesical treatment and follow-up in all cases.

Endovesical treatment, performed with the aim of delaying tumor progression and preserving the bladder, was started 4 weeks after TUR. Follow-up was performed to assess both the safety (tolerability and toxicity) and efficacy (recurrence and progression) of GEM versus BCG endovesical treatments.

Local and systemic toxicity was recorded during structured interviews: urinary symptoms and bother (dysuria, hematuria, frequency/urgency, urinary incontinence) and systemic adverse events (fever, asthenia, cardiovascular discomfort, gastrointestinal dysfunction) were reported. Blood tests, urinalyses and urine cultures were routinely performed before the first 3-month follow-up. Cystoscopy and urinary cytology were performed 4 weeks after completion of the first 6 weeks of endovesical treatment. In tumor-free cases, cystoscopy and urinary cytology were repeated at 3-month intervals for the first 2 years, at 6-month intervals for the next 3 years and yearly thereafter. Recurrence was defined as the appearance of a new tumor either of lower tumor classification and grade (pTaG1, G2), or of the same pT1G3 pattern, while progression was defined by the depth of bladder muscle invasion or by local, regional or distant metastases according to TNM 1997, as defined by the American Joint Committee on Cancer and WHO grade [19]. The time to first recurrence (disease-free interval) was defined as the time from surgery (TUR) until the first cystoscopy at which a recurrence was observed.

Statistics

Progression-free survival was estimated by the Kaplan-Meier product limit method. Comparison between GEM and BCG groups was made using the log-rank test and significance level was set to a p value of 0.05. All statistical analyses were performed using SPSS 10.0 for Apple-Macintosh (SPSS, Inc., Chicago, Ill., USA).

Results

Both intravesical administration of GEM and BCG were generally well tolerated; no severe adverse events were reported in patients enrolled in the study. One pa-

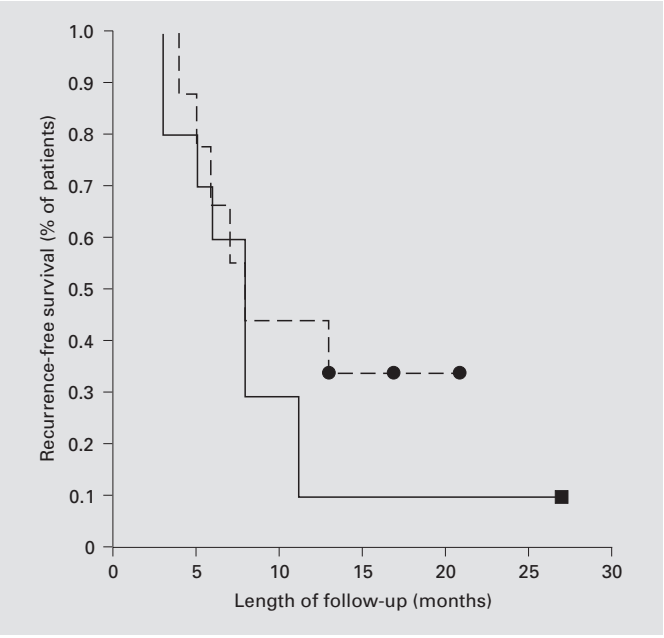

Fig. 1. Kaplan-Meier curves show time to recurrence for 9 GEM patients (– – –) and 10 BCG patients (——): difference was not statistically significant (log-rank test p = 0.328).

tient from the GEM group reported fever (<38°C) in the induction course and during the first three administrations which regressed after subsequent instillations, while another patient experienced only minimal irritative urinary symptoms that lasted for 24 h. Seven of 9 patients did not report any adverse events. Regular blood tests, urinalyses and urine cultures, performed at the end of the 6-week induction course, demonstrated the absence of acute or chronic systemic toxicity. Two patients from the BCG group reported fever (<38°C) during the induction course and during all six administrations, but not during the maintenance course. One patient with hematuria recovered within 48 h, while another patient had grade-1 dysuria which lasted for 2 days. Six of 10 patients did not report any local or systemic toxicity. Hematological and urinary checks were all in the normal range.

Of the 9 patients treated with GEM, 6 had recurrences after 4–19 months and were once more treated with TUR of the bladder tumor (TURBT): 4 still had superficial bladder tumors (2 pTaG2, 2 pT1G1) and underwent further endovesical GEM administration, while 2 patients with tumor progression at TURBT (2 pT2G3) underwent radical cystectomy with bladder reconstruction (patient 2G) and radical cystectomy with ureterocutaneostomy (patient 8G). These patients were free of tumor recurrence after 5 and 2 months. Three patients were recurrence-free 13, 17 and 21 months after GEM administration. On the whole, 7 of 9 patients have kept an intact bladder, and the overall survival rate is 9 of 9.

Among 10 patients treated with BCG instillation, 9 recurred after 3–13 months and were treated with further TURBT: 5 patients who again had superficial TCC received a new cycle of BCG, while 4 patients with tumor progression (2 pT2G3, 1 pT3bG3 and 1 pT4G3) were treated with partial cystectomy and adjuvant chemotherapy (patient 10B), and radical cystectomy with ureterocutaneostomy (patients 3B, 4B and 6B). Of these last 4 patients, 2 died at 15 and 16 months after the last BCG course, while 2 are still alive without recurrence after 8 and 11 months. Only 1 patient was recurrence-free 27 months after another course of BCG. Therefore, 6 of 10 patients have retained their bladders, with a survival rate of 8 of 10.

Discussion

Poorly differentiated (G3) TCCs, invading the lamina propria (pT1), usually have a poorer prognosis than other superficial bladder tumors, with recurrence and progression rates after TUR alone of 50–70 and 25–50%, respectively [20]. Therefore, some authors recommend early radical cystectomy for these patients, reporting a 5-year survival rate between 70 and 90% if performed immediately, and 50–60% if delayed [21]. However, though a radical approach may be the best chance to cure patients with pT1G3 TCC, many of them prefer conservative treatment, and furthermore, many patients are unsuitable for a radical cystectomy owing to age or associated comorbid medical illness.

To reduce tumor recurrence and progression after TURBT, adjuvant BCG instillation is used as first-line treatment. Many studies reported a recurrence and progression rate after BCG adjuvant therapy of 16–52 and 7.7–22.8%, respectively [22]. A multicentric retrospective trial with a 17-year follow-up demonstrated a 5-year survival of 80% for pT1G3 patients treated with BCG, and 87% bladder maintenance, allowing good middle term cancer control with excellent quality of life [23]. However, longer follow-up has demonstrated a progression risk of 16% between 5 and 10 years and 12% for 10–15 years [24]. Nevertheless, even if there are many

different definitions of BCG refractory disease, 43% of patients have a residual tumor after standard TURBT plus BCG, and after a new BCG administration 20% of patients can be defined as truly BCG refractory [15]. In a retrospective study on recurrent pT1G3 bladder TCC, Baniel et al. [25] demonstrated that after a second BCG course only one third of the patients were disease-free and the mean time to recurrence was 22 months; furthermore, only 3 of 22 (13.6%) patients remained disease-free after a third induction of BCG. Moreover, patients with recurrence before 21 months after the first BCG course are not likely to benefit from another course of BCG [26]. Therefore, patients with tumor recurrence after BCG and especially those with an early recurrence should be considered for alternative therapies.

Many new experimental modalities are now available for treating patients with superficial bladder cancer who have failed BCG: optimized chemotherapy with mitomycin C (electromotive or with hyperthermia), interferon-α2B alone or combined with BCG and GEM have shown some promising results, even though randomized phase-II and -III trials are still lacking [27].

GEM is a well-tolerated anti-cancer drug that could be a valid treatment option for those patients who choose further conservative treatment after BCG failure. Laufer et al. [28] have previously demonstrated the safety and efficacy of GEM in endovesical adjuvant administration. Furthermore, Dalbagni et al. [29] recently demonstrated the excellent results of endovesical GEM as second- or third-line treatment on BCG-refractory TCC patients refusing cystectomy.

In the light of the efficacy and tolerability of GEM, we proposed a conservative approach in a very select population of patients affected by BCG-refractory pT1G3 TCC of the bladder, unsuitable for cystectomy, and we compared our results with those of an analogous population of patients treated with a further course of BCG. Our data confirm the high tolerability of endovesical administration of GEM in patients previously treated with TURBT plus BCG courses. In particular, we only report 1 case of fever and 1 of irritative urinary symptoms which were minimal, transitory and local, and no significant systemic toxicity was reported by any of the patients both for induction and maintenance courses. Our short-term oncological results demonstrate a complete response (negative post-treatment cystoscopy and negative cytology) for one third of the patients, while only 1 of 10 patients retreated with BCG was disease-free. Recurrence occurred in 4 of 9 patients treated with GEM compared to 5 of 10 patients treated with BCG.

An attractive oncological outcome was the fairly low tumor progression rate in patients treated with GEM compared to BCG: only 2 patients with TCC progressed after GEM while 4 patients progressed after reiterated BCG. Furthermore, invasive bladder tumors after GEM were all pT2, while after a second course of BCG tumors progressed to pT3 and pT4. However, all the data regarding tumor progression are worthless due to the absence of a second TUR that could confirm the absence of a preexistent infiltrating neoplasm.

The overall follow-up of the study is actually limited (mean 19 and range 7–27 months); however, for all patients included in the study follow-up time was appreciably longer than the time from the last recurrence, with mean differences of 11 and 13 months for the GEM and BCG groups, respectively (compare the 6th with the 14th column in tables 1 and 2). Furthermore, pT1G3 BCG-resistant TCCs of the bladder are neoplasms with a fast evolution, resulting in a very short time to recurrence or progression due to the their characteristic aggressiveness. A descriptive analysis of our data reveals that the mean time to recurrence after GEM (6.5 months) was quite shorter than after repeated BCG (8.2 months), while time to progression was longer (8.5 vs. 5.5 months for GEM vs. BCG), even if any accurate statistical analysis can be performed on this small population.

The restricted population of patients, the short follow-up and the absence of randomization are the limits of our report. However, this pilot study describes the first experience concerning an attractive application of endovesical treatment with GEM.

Conclusions

Our experience confirms the high risk of tumor recurrence and progression of BCG-refractory pT1G3 TCC. In these cases, the choice of radical cystectomy must be considered mandatory, allowing some chance of cure, while all conservative treatments after BCG failure should be defined experimentally.

In our restricted population, further BCG courses seem to be unsuitable for patients who have already failed two BCG courses, resulting in a high risk of tumor progression and mortality.

The use of GEM in BCG-refractory pT1G3 patients has to be considered investigational, until multicentric randomized studies with adequate follow-up have confirmed the preliminary results of this pilot study.

References

1 Soloway MS, Sofer M, Vaidya A: Contemporary management of stage T1 transitional cell carcinoma of the bladder. J Urol 2002;167: 1573–1583.
2 Gottengo B: T1G3 Bladder cancer: conservative management or cystectomy? Eur Urol 2004;45:339–400.
3 Thalmann G, Markwalder R, Shahin O, Burkhard F, Hochreiter W, Studer U: Primary T1G3 bladder cancer: organ preserving approach or immediate cystectomy? J Urol 2004; 172:70–75.
4 Patard J, Moudouni S, Saint F, Rioux-Leclercq N, Manunta A, Guy L, Ballanger P, Lanson Y, Hajri M, Irani J, Guille F, Beurton D, Lobel B: Tumor progression and survival in patients with T1G3 bladder tumors: multicentric retrospective study comparing 94 patients treated during 17 years. Urology 2001;58:551–556.
5 Pansadoro V, Emiliozzi P, de Paula F, Scarpone P, Pansadoro A, Sternberg CN: Long-term follow-up of G3T1 transitional cell carcinoma of the bladder treated with intravesical bacilli Calmette-Guérin: 18-year experience. Urology 2002;59:227–231.
6 Bohle A, Bock PR: Intravesical bacille Calmette-Guérin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumor progression. Urology 2004;63:682–687.
7 Saint F, Salomon L, Quintela R, Cicco A, Abbou CC, Chopin DK: Classification, favorable characteristics, prevention and treatment of adverse side effects associated with bacillus Calmette-Guérin in the treatment of superficial bladder cancer. Ann Urol 2002;36:120–131.
8 Rintala E, Jauhiainen K, Kaasinen E, Nurmi M, Alfthan O: Alternating mitomycin C and bacillus Calmette-Guérin instillation prophylaxis for recurrent papillary (stages Ta to T1) superficial bladder cancer. Finnbladder Group. J Urol 1996;156:56–60.
9 Bilen CY, Ozen H, Aki FT, Aygun C, Ekici S, Kendi S: Clinical experience with BCG alone versus BCG plus epirubicin. Int J Urol 2000; 7:206–209.
10 Steinberg G, Bahnson R, Brosman S, Middelton R, Wajsman Z, Wehle M: 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 2000;1633:761–767.
11 Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997;15:2403–2413.
12 Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J, Johnson DH, Eastern Cooperative Oncology Group: Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92–98.
13 Moore MJ, Tannock IF, Ernst DS, Huan S, Murray N: Gemcitabine: a promising new agent in the treatment of advanced urothelial cancer. J Clin Oncol 1997;15:3441–3445.
14 Cozzi PJ, Bajorin DF, Tong W, Nguyen H, Scott J, Heston WD, Dalbagni G: Toxicology and pharmacokinetics of intravesical gemcitabine: a preclinical study in dogs. Clin Cancer Res 1999;5:2629–2637.
15 Herr HW, Dalbagni G: Defining bacillus Calmette-Guérin refractory superficial bladder tumors. J Urol 2003;169:1706–1708.
16 Pagano F, Garbeglio A, Milani C, Bassi P, Pegoraro V: Prognosis of bladder cancer. I. Risk factors in superficial transitional cell carcinoma. Eur Urol 1987;13:145–151.
17 Palou J, Carcas A, Segarra J, Duque B, Salvador J, Garcia-Ribas I, Villavicencio H: Phase I pharmacokinetic study of a single intravesical instillation of gemcitabine administered immediately after transurethral resection plus multiple random biopsies in patients with superficial bladder cancer. J Urol 2004;172:485–488.
18 Jakse G, Algaba F, Malmstrom PU, Oosterlinck W: A second-look TUR in T1 transitional cell carcinoma: why? Eur Urol 2004;45:539–546.
19 Epstein JI, Amin MB, Reuter VR, Mostofi FK: The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Am J Surg Pathol 1998;23:1435–1448.
20 Jakse G, Loidl W, Seeber G, Hofstadter F: Stage T1 grade 3 transitional cell carcinoma of the bladder: an unfavourable tumor? J Urol 1987;137:39–43.
21 Bracken RB, McDonald MW, Johnson DE: Cystectomy for superficial bladder cancer. Urology 1981;18:459–463.
22 Peyromaure M, Zerbib M: T1G3 transitional cell carcinoma of the bladder: recurrence, progression and survival. BJU Int 2004;93:60–63.
23 Patard J, Moudouni S, Saint F, Rioux-Leclercq N, Manunta A, Guy L, Ballanger P, Lanson Y, Hajri M, Irani J, Guille F, Beurton D, Lobel B, Bernard Lobel and the members of the Groupe Necker: Tumor progression and survival in patients with T1G3 bladder tumors: multicentric retrospective study comparing 94 patients treated during 17 years. Urology 2001;58:551–556.
24 Herr HW: Tumour progression and survival in patients with T1G3 bladder tumours: 15-year outcome. Br J Urol 1997;80:762–765.
25 Baniel J, Grauss D, Engelstein D, Sella A: Intravesical bacillus Calmette-Guérin treatment for stage T1 grade 3 transitional cell carcinoma of the bladder. Urology 1998;52:785–789.
26 Bretton PR, Herr HW, Kimmel M, Whitmore WF Jr, Laudone V, Oettgen HF, Fair WR: The response of patients with superficial bladder cancer to a second course of intravesical bacillus Calmette-Guérin. J Urol 1990;143:710–713.
27 Joudi FN, O'Donnell MA: Second-line intravesical therapy versus cystectomy for bacille Calmette-Guérin (BCG) failures. Curr Opin Urol 2004;14:271–275.
28 Laufer M, Ramalingam S, Schoenberg MP, Haisfield-Wolf ME, Zuhowski EG, Trueheart IN, Eisenberger MA, Nativ O, Egorin MJ: Intravesical gemcitabine therapy for superficial transitional cell carcinoma of the bladder: a phase I and pharmacokinetic study. J Clin Oncol 2003;21:697–703.
29 Dalbagni G, Russo P, Sheinfeld J, Mazumdar M, Tong W, Rabbani F, Donat MS, Herr HW, Sogani P, dePalma D, Bajorin D: Phase I trial of intravesical gemcitabine in bacillus Calmette-Guerin-refractory transitional-cell carcinoma of the bladder. J Clin Oncol 2002; 20:3193–3198.