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Original article

Intravesical Gemcitabine for Treatment of Superficial Bladder Cancer not Responding to Bacillus Calmette-Guérin Vaccine

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ABSTRACT

Objectives: Intravesical Bacillus Calmette-Guérin (BCG) vaccine is the mainstay of treatment and prophylaxis in superficial bladder cancer (SBC) as it reduces tumor recurrence and disease progression. About one-third of patients do not respond to BCG. The aim of this study was to determine the efficacy of intravesical gemcitabine in patients with BCG-refractory SBC.

Methods: Twenty three patients with SBC; TaG3, T1G2-G3 or carcinoma in situ (CIS), refractory (after at least 2 courses of intravesical BCG) or intolerant to intravesical BCG therapy were included. Two weeks after complete tumor resection, patients received intravesical gemcitabine twice weekly at a dose of 2.000 mg/100 ml normal saline for 6 consecutive weeks. Two months after the last dose, recurrence-free patients underwent cystoscopy, urinary cytology and 6 random bladder biopsies. Thereafter, patients were evaluated by the same measures every 3 months, as long as there was no recurrence. Patients with complete response (negative cytology and random biopsies) at the first follow-up cystoscopy received a similar maintenance dose once weekly for another 6 weeks.

Results: Twenty one patients completed the study: 15 males and 6 females with a mean age of 48.1 (38-72) years. The follow-up was 15 months (range 2-19 months). Thirteen (61.9%) patients were recurrence-free after a mean of 17 months. Superficial recurrences were detected in 6 (28.6%) patients and progression by stage in 2 patients (9.5%). During follow-up, 8 patients had tumor recurrences and 2 had progression to a higher stage. The median recurrence-free time was 14.7 months (5-19 months). The drug was well tolerated and side-effects were mild in all patients, except two: one had easily controlled hematuria and the other had leucopenia.

Conclusion: In properly selected patients, gemcitabine seems to be a promising option in the management of high-risk BCG-refractory SBC, especially in those who refuse or are unfit for cystectomy. Long-term efficacy and the role of maintenance therapy have to be properly studied.

Key Words: Superficial bladder cancer, BCG, gemcitabine, intravesical

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INTRODUCTION

Bladder cancer is a heterogeneous disease with a variable natural history. On average, 70% of bladder tumors present as non–muscle-invasive bladder cancer (NMIBC)[1]. Recurrence rates after initial treatment range from 30% to 85%, with grade progression occurring in 10% to 30% and stage progression in 4% to 30% of cases[2]. This high rate of recurrence and progression can be reduced with intravesical therapy after proper complete transurethral resection of the bladder tumor (TURBT)[3]. Intravesical bacillus Calmette-Guérin (BCG) vaccine is the mainstay of superficial bladder cancer

(SBC) treatment in terms of reduction of tumor recurrence and disease progression[4]. Unfortunately, about one-third of patients do not respond to BCG, which represents a significant challenge[5]. Gemcitabine is an active systemic chemotherapeutic agent in the management of advanced bladder cancer and it has also been evaluated in the management of superficial disease. The aim of this study was to determine the efficacy of gemcitabine hydrochloride administered as intravesical agent in patients with BCG-refractory/intolerant SBC.

PATIENTS AND METHODS

Twenty three patients were included in the study after fulfilling the inclusion criteria. Informed consent was signed by all patients after being informed about the study, different management options, the possibility of response, and the side-effects of the drug. The inclusion criteria were: (1) histologically proven recurrent superficial transitional cell carcinoma (TCC) of the bladder (TaG3, T1G2-3, or CIS); (2) at least two previous courses of failed intravesical BCG (or intolerance to intravesical BCG therapy) ± one course of chemotherapy other than gemcitabine; (3) no previous gemcitabine therapy; (4). no other malignancy apart from the existing bladder tumor; (5) Females must neither be pregnant nor lactating. Two weeks after TURBT, patients received intravesical gemcitabine twice weekly at a dose of 2.000 mg/100 ml normal saline for 6 consecutive weeks. Gemcitabine was instilled via a Foley transurethral catheter and remained in the bladder for 2 hours. Patients were advised to change their position in bed from time to time. Complete emptying of bladder was done routinely prior to therapy in order to improve therapeutic efficacy. Patients were asked to restrict fluid intake and to take systemic alkalinizer one day before therapy for better absorption of gemcitabine. Blood tests (complete blood count (CBC), liver enzymes, and serum creatinine) were performed before gemcitabine therapy and before each cystoscopy. Two months after the last dose, patients underwent cystoscopy, urinary cytology and 6 random bladder biopsies if there was no visible recurrence. Thereafter, recurrence-free patients were evaluated by the same measures every 3 months. Patients who revealed complete response after the first follow-up cystoscopy (in terms of negative cytology and random biopsies) received a maintenance similar dose once weekly for another 6 consecutive weeks. The following variables were recorded for every patient: age and sex, previous intravesical therapy with response and tolerance, pathological stage before start of gemcitabine therapy, cystoscopy status and date, response to intravesical gemcitabine, time of recurrence and/or progression and toxicity of the drug. Complete response (CR) was defined as absence of suspicious lesions on cystoscopy and/or negative biopsies and cytology. Recurrence-free survival time is the time from the date of response to therapy to the date of recurrence or last follow-up. Time to progression is from the date of response to therapy to the date of progression or cystectomy.

RESULTS

Twenty one patients completed the study: 15 males and 6 females with a mean age of 48.1 (38-72) years. Two patients were lost to follow-up early during induction therapy. The median duration of follow-up was 15 months (ranging from 2-19 months). Patient data are shown in Table 1. Thirteen (61.9%) patients had T1G2-3 TCC ± CIS, 5 (23.8%) patients had CIS and 3 (14.3%) patients had high grade Ta TCC. The efficacy of intravesical gemcitabine is shown in Table 2. During follow-up 8 patients had tumor recurrence and 2 of them had progression to a higher stage. Figure 1 shows the response to gemcitabine as regards pathological stage and grade during follow-up. The superficial recurrences occurred early (after 2 months in 2 patients) which represents non-response to gemcitabine. Other recurrences were detected at 5 months in one patient, 14 months in 2 patients, and 17 months in one patient. Two patients in this category underwent radical cystectomy and

Table 1: Pre-gemcitabine pathologic stage and grade of the study patients.

Stage	No (%)
TaG3	3 (14.3)
T1 G2	4 (19.0)
T1 G3	9 (42.9)
CIS	5 (23.8)
Total	**21 (100)**

the other 4 were followed up with cystoscopy. Stage progression was detected in 2 patients, at 8 and 11 months after starting intravesical therapy. Both patients progressed to muscle invasive disease; one underwent radical cystectomy, the other was unfit for surgery and died 2 months later. Complete response was present in 13 (61.9%) patients up to 19 months of follow-up.

The median recurrence-free time was 14.7 months (5 to 19 months). The drug was tolerable and side-effects were mild in most patients, apart from two patients; one had easily controlled hematuria and the other had leucopenia. Four patients developed cystitis syndrome, but their symptoms were easily controlled and did not affect treatment strategy.

DISCUSSION

Treatment of SBC aims to eradicate existing disease and to prevent tumor recurrence and/or progression to muscle invasion and metastasis. Patients treated only by TURBT have a 49% chance of remaining free of disease[6]. Intravesical chemotherapy and immunotherapy have resulted in significant reduction in the risk of disease recurrence. SBC lends itself to intravesical therapy due to the potential for direct contact between chemotherapeutic drug and tumor. Furthermore, very high concentrations of agents can be achieved in the bladder with minimal systemic toxicity[7]. BCG immunotherapy has become the standard

Table 2: Efficacy of intravesical gemcitabine in the study patients.

Results	No (%)
Recurrence-free	13 (61.9)
Superficial recurrence	6 (28.6)
Progression	2 (9.5)
Total	**21 (100)**

treatment for high-risk SBC, including T1G3, CIS and some recurrent Ta cases[4]. However, BCG treatment fails in 30-40% of patients, and 30-40% of those who initially respond, eventually relapse[8]. Peyromaure and coworkers reported 42% and 28% recurrence and progression rates, respectively, in 57 patients followed up for 53 months[9]. Shahin and associates found that 70% of their patients recurred after BCG, versus 75% treated with TURBT alone[10]. These results have led many authors to advocate early cystectomy for T1G3 SBC, particularly in the presence of unfavorable prognostic factors[11]. Hence, BCG is not always effective and response is not always durable. Failure to achieve a complete response following BCG induction predicts poor prognosis, including a 67% higher risk of death. Risk factors reported for non-response, recurrence or progression include increased numbers of tumors, large tumor size, older age, prior recurrence, more advanced stage or grade, and the presence of CIS. Radical cystectomy can be the first treatment of choice for young, otherwise healthy patients with high-grade T1 disease, or patients with multifocal CIS who cannot tolerate BCG. The 5-year disease-free survival rate with radical cystectomy is approximately 85% for patients with pathologic node-negative T1 tumors (pT1) and 95% for stage pTa or pCIS tumors, making radical cystectomy an excellent initial treatment for selected high-risk patients[12]. the significant limitations in efficacy and tolerability for the most widely used intravesical drugs across all risk categories of SBC have favored the search for new treatment alternatives[4]. In the past few years, new drugs have been investigated that may play a future role in this indication[13].

Table 3: Studies of intravesical gemcitabine in intermediate and high risk SBC.

Authors	No Pts	Schedule	MFU month	RF	SR	Prog.
Dalbagni et al[24]	18	Twice weekly for 3 wks, repeated after a week of rest	2	7	4 PR	NS
Montella et al[20]	9	4 wks before and 4 wks after TURBT	17	2	7	0
Bounedjar et al[22]	118	6 wks induction + Maint. 3 weekly at 3, 6, 12, 18, 24, 30, 36 months	12	85	29	NS
Gontero et al[17]	30	Twice weekly for 3 wks, repeated after a week of rest	19	2	12 (+7 PR)	1
Dalbagni et al[18]	9	NS	21	3	6	0
Gunelli et al[25]	40	Twice weekly/ 6wks	28	14	14	0
Bounedjar et al[26]	60	Once weekly / 6wks + Monthly/ 6 months	39	53	5	2
Gontero et al[4]	35	Once weekly / 6wks	18	21	11	3
Gacci et al[19]	48	Once weekly / 6wks	NS	42	0	6
Mattioli et al[21]	60	6 wks induction + monthly dose/ 6 months	60	23	26	6

This study evaluated the efficacy of intravesical gemcitabine as a chemotherapeutic agent in patients with BCG-refractory SBC. Systemic chemotherapy with gemcitabine and cisplatin for locally advanced muscle-invasive bladder cancer has shown promising results[14,15] with low side-effects and good tolerability as an alternative treatment option to conventional radical cystectomy. Gemcitabine, a deoxy-cytidine analogue, has a broad-spectrum anti-tumor activity. Being a non-vesicant drug, it has very little local toxicity, therefore a high concentration in the bladder can be achieved without drug-induced cystitis. It penetrates the bladder mucosa well, due to its low molecular weight of 299 Da and preferentially produces cytotoxicity in bladder cancer cells while sparing non-transferred bladder mucosa and submucosal cells. Its rapid transformation into an inactive metabolite prevents systemic toxicity[5]. No systemic absorption with a clinical or pharmacological effect was detected and only slight irritative bladder symptoms were observed[16]. Intravesical gemcitabine has shown an excellent safety profile with minimal toxicity at concentrations up to 40 mg/ml and this should therefore be the standard dose for any future study[4]. Instillation times of one and two hours have both been tested with excellent tolerability[17]. However, instillation over 2 hours seems to be a feasible option and might be better than instillation for 1 hour[4]. In this study the recommended dose and instillation time had been planned. Table 3 shows some studies investigating the activity of intravesical gemcitabine in intermediate and high-risk SBC. It has to be mentioned that comparison between the results of those studies could not be done because they have different methodologies as regards patients' data, the dose and schedule of drug administration, and the planning of maintenance therapy. In the phase II study of Dalbagni and colleagues,

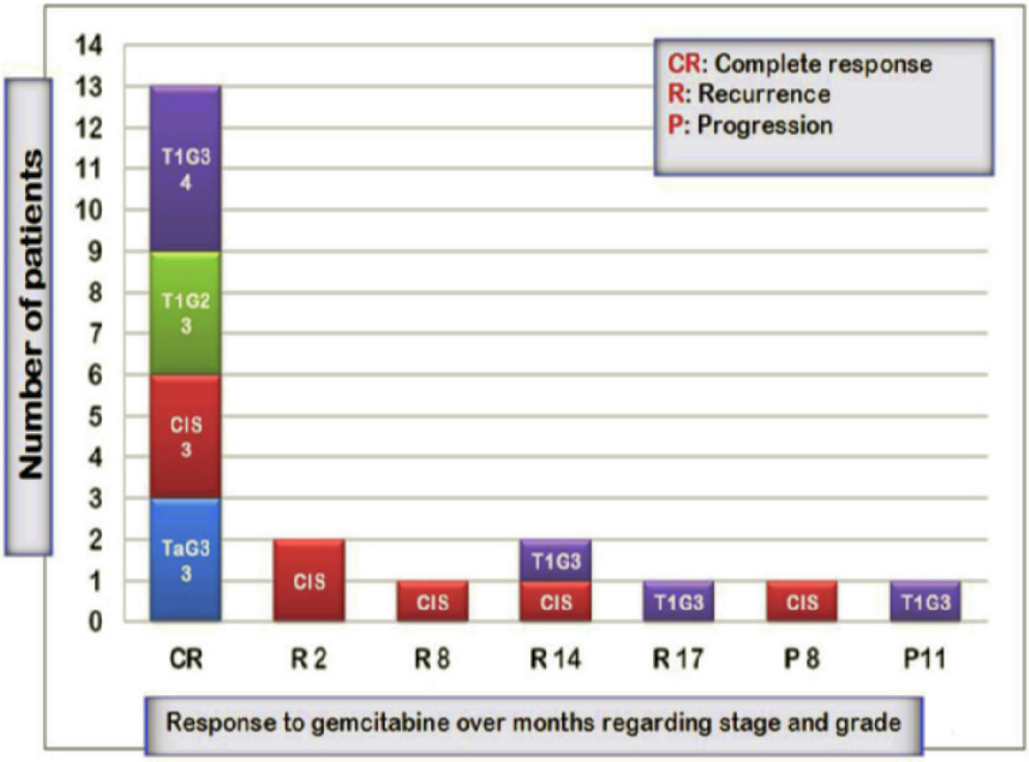

Fig. 1: Response of the patients to intravesical gemcitabine over months as regard to the pathological stage and grade.

30 eligible patients were included with a median follow-up of 19 months (range, 0 to 35 months). Of the 30 patients, 15 achieved CR, of whom only 2 patients maintained CR at 23 and 29 months, respectively[18]. These differences from our results could be related to two main causes; firstly, differences in the primary grade and stage of the SBC (23/30 patients were CIS). Secondly, the difference in methodology, as the patients in the phase II study received only two courses of intravesical gemcitabine twice weekly for 3 consecutive weeks, with each course separated by one week of rest without maintenance. The role of maintenance therapy should be investigated in future studies. Mohanty et al reported that 21 (60%) patients showed no recurrences, 11 (31.4%) had superficial recurrences while 3 (8.6%) progressed to muscle invasiveness[5]. Average time to first recurrence was 12 months and to disease progression was 16 months[5]. No maintenance therapy was planned in that study and the higher response rate was due to 18 (50%) of patients with low grade Ta TCC. Gacci and others confirmed the high risk of tumor recurrence and progression of BCG-refractory pT1G3 TCC and recommended that further BCG courses seem to be unsuitable, resulting in a high risk of tumor progression and mortality[19]. Of the 9 patients treated with gemcitabine, 3 were recurrence-free after 13, 17 and 21 months. The authors concluded that the use of gemcitabine in BCG-refractory pT1G3 patients has to be considered experimental until multicentre randomized studies with adequate follow-up are able to confirm their preliminary results[19]. The low response rate to gemcitabine in that series may be the result of the smaller sample size and the fact that all patients had stage pT1G3 tumours. In our study and that of Mohanty and colleagues[5], there were some patients who had pTaG3 and pT1G2 whose response to gemcitabine might have been much better. Montella and others studied intravesical gemcitabine versus mitomycin-C (MMC) for recurrent SBC. In the gemcitabine group 42 (78%) patients remained free of recurrence compared to 37 (67%) patients in the MMC group (p=0.05). Ten patients in the MMC

arm and 6 in the gemcitabine group had progressive disease by stage. The authors concluded that intravesical therapy with gemcitabine is active and better tolerated than MMC in refractory TCC patients[20]. The higher rate of response to gemcitabine in the previous series over all other published data was because all patients had low-grade, low-stage disease (Ta-T1G1-G2). In the series of Mattioli and associates, one patient had recurrence 1 month after TURBT, 3 patients between 3 and 6 months, and another 3 after 8, 11 and 18 months and 2 were recurrence-free after 21 and 22 months, respectively[21]. Their results could not be compared to that of the present study as their sample was relatively small (9 patients). Also, the authors' methodology was different in that gemcitabine was administered once a week in the 4 weeks before and the 4 weeks after TURBT. Moreover, the pathologic stages and grades of their patients were not presented. Smaili and colleagues presented the results at 5 years of intravesical gemcitabine single agent as adjuvant chemotherapy in superficial TCC of the bladder[22]. Sixty patients (9 had CIS and 51 had pT1) received intravesical instillation of gemcitabine once weekly for 6 weeks, then every month for 6 months. They found that 23 (38.3%) patients had a persistent CR after treatment, 26 (43.3%) had superficial relapse of TCC, and 6 (10%) had progressive disease[22]. The authors used a different and unique protocol for maintenance therapy. Bartoletti and colleagues performed a multicentric study of 118 patients followed for a mean of 12 months; 85 (74.6%) were recurrence-free and 29 (25.4%) showed superficial recurrences[23]. Intravesical gemcitabine is well tolerated, associated with minimal systemic absorption and has a moderate efficacy in the treatment of SBC[17-20]. In this study, intravesical gemcitabine was well tolerated with mild side-effects in most patients. One patient had easily controlled hematuria, another one had leucopenia. Four patients developed cystitis syndrome, but their symptoms were easily controlled and did not affect treatment strategy. Gemcitabine has low and transient adverse events and excellent cytotoxic effect with the result that more intense treatment schedules are now being contemplated. The ongoing phase II studies would provide additional information to predict the efficacy of gemcitabine in clinical practice and constitute the framework for large comparative phase III studies.

Conclusions

Gemcitabine appears to be a promising option in management of high-risk patients with BCG-refractory SBC especially those who refuse or unfit for cystectomy. Long-term efficacy and the role of maintenance therapy have to be properly investigated. The question now not about the efficacy of the drug but which group of patients could be selected for this treatment strategy?

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