Is gemcitabine an option in BCG-refractory nonmuscle-invasive bladder cancer? A single-arm prospective trial

Sisto Perdonà[a], Giuseppe Di Lorenzo[b], Francesco Cantiello[f], Rocco Damiano[f], Marco De Sio[c], Daniele Masala[d], Gianni Bruni[e], Luigi Gallo[a], Piera Federico[b], Carmelo Quattrone[c], Mariano Pizzuti[c] and Riccardo Autorino[c]

The objective of this study was to evaluate intravesical gemcitabine in high-risk nonmuscle-invasive bladder cancer (NMIBC) refractory to bacillus Calmette-Guérin (BCG). This was a prospective multicentre single-arm trial. Eligible patients were those with high-risk NMIBC refractory to BCG therapy, for which radical cystectomy was indicated but not conducted because of patient refusal or ineligibility. Patients received intravesical gemcitabine twice weekly at a dose of 2000 mg/50 ml for 6 weeks, and then weekly for 3 weeks at 3, 6, and 12 months. Outcome measures were recurrence rate, time to first recurrence, progression rate and complications. Twenty patients were enrolled and included in the analysis. Median follow-up was 15.2 months. Fifty-five percent (11 patients) developed disease recurrence. Mean time to the first recurrence was 3.5 months and 45% (five patients) of recurring patients had disease progression. Overall, treatment was well tolerated. Urinary symptoms represented the primary adverse events. The role of gemcitabine used as second-line treatment in high-risk BCG-refractory NMIBC patients who refused or were unsuitable for radical cystectomy remains to be defined. Further clinical research in this area is needed. ***Anti-Cancer Drugs*** **21:101–106 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2010, **21**:101–106

Keywords: bacillus Calmette-Guérin, failure, gemcitabine, nonmuscle-invasive bladder cancer

[a]UOC Urologia, INT Fondazione Pascale, [b]Dipartimento di Oncologia Molecolare e Clinica, Università Federico II, [c]Clinica Urologica, Seconda Università degli Studi, [d]UOC Urologia, Ospedale Cardarelli, [e]UO Oncologia Medica e Terapie Innovative, INT Fondazione Pascale, Napoli and [f]UOC Urologia, Università Magna Graecia, Catanzaro, Italy

Correspondence to Dr Riccardo Autorino, MD, PhD, FEBU, Clinica Urologica, Seconda Università degli Studi, Piazza Miraglia, 2–80138, Napoli, Italy
Tel: +39 335 841 6713; fax: +39 081 899 7274; e-mail: ricautor@tin.it

Sisto Perdonà, Giuseppe Di Lorenzo and Riccardo Autorino have contributed equally to the study

Received 16 July 2009 **Revised form accepted** 26 August 2009

Introduction

Bacillus Calmette-Guérin (BCG) therapy is associated with a reduced risk of tumour progression and recurrence in patients with high-risk nonmuscle-invasive bladder cancer (NMIBC) compared with chemotherapy [1–3]. In 20–40% of patients, BCG therapy apparently fails resulting in recurring tumours, depending on the follow-up time and their initial risk profile [4]. When BCG is used as therapy, it induces a 70% initial complete response rate, which remains in only 50% of patients after long follow-up [5]. Looking at patients who showed progression after BCG treatments, Sylvester *et al.* [1] reported a cancer-specific death rate of 64% at 2.5 years. Similar outcomes were found by others [6].

Thus, the window of opportunity for these patients remains limited. Three months of BCG therapy can be administered, given that this regimen is associated with a complete response in more than 50% of patients [7]. Changing from BCG to chemotherapy can provide further remissions in selected patients. However, in most high-risk BCG failures, immediate cystectomy is advocated [8]. Some of these patients cannot be submitted to radical surgery because of unacceptable anaesthesiological risks and/or patient refusal; therefore, more-conservative approaches might be considered [9,10].

Gemcitabine represents the standard in systemic therapy for advanced bladder cancer [11]. Given its pharmacokinetic properties, gemcitabine has also been suggested as an ideal candidate for intravesical use [12]. Intravesical gemcitabine was first reported as a new treatment option for BCG-refractory NMIBC patients by Dalbagni *et al.* [13] in a pioneering phase I study. More recently, the same group reported a phase II study assessing the efficacy of gemcitabine administered as an intravesical agent in BCG-refractory patients refusing cystectomy [14]. We aimed to evaluate the efficacy of intravesical gemcitabine in high-risk BCG-refractory NMIBC patients who refused or were unfit for radical cystectomy.

Materials and methods

This was a multicentre prospective single-arm phase II trial carried out between July 2006 and July 2008. The study was conducted after obtaining institutional review board approval. Written informed consent was obtained from all patients.

Inclusion criteria

Eligible patients were those with high-risk NMIBC [15] who were refractory to BCG therapy (failure to achieve disease-free state by 6 months after initial BCG therapy

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with either maintenance or re-treatment at 3 months because of either persistent or rapidly recurring disease [7,16]) and for whom radical cystectomy was indicated but not conducted because of patient refusal or ineligibility caused by comorbidities. All patients had received their perioperative chemotherapy instillation after their primary transurethral resection (TUR) of the bladder. The applied BCG schedule followed the Southwest Oncology Group recommendation (induction course consisting of 6 weekly instillations and maintenance course of 3 weekly instillations at 3, 6, and 12 months). Exclusion criteria were concurrent or previous muscle-invasive disease, concurrent or previous tumour in the upper urinary tract or prostatic urethra, chronic urinary tract infection, cured or active tuberculosis, any other malignancy, previous pelvic irradiation, creatinine and transaminase concentrations higher than twice the standard, pregnancy/lactation and any other disease with immunodeficiency.

Treatment and follow-up

Two thousand milligrams of gemcitabine (Gemzar, Eli Lilly) was diluted in 50 ml of normal saline (0.9%), with a final concentration of 40 mg/ml, and then instilled in the bladder. The pH of the reconstituted solution varied between 2 and 3 and no buffering was adopted. The patients were asked to avoid urinating for 1 h after the instillation.

Patients started treatment 4–6 weeks after the last TUR, receiving intravesical gemcitabine twice weekly (days 1 and 4) at a dose of 2000 mg/50 ml for 6 consecutive weeks (induction course) and then weekly for 3 consecutive weeks at 3, 6, and 12 months.

The prestudy clinical evaluation comprised medical history, general physical examination, electrocardiogram, computed tomography–urography scan, chest radiograph and haematological evaluation. A urine analysis with urine culture was also carried out weekly during the treatment. Cytological analysis of voided urine and cystoscopy were performed at 3-month intervals. Intravenous urography or computed tomography–urography was performed annually.

Outcome measures

Recurrence was determined by lesions that were detected at cystoscopy and pathologically confirmed after TUR. Positive cytology alone was not considered a recurrence. In the case of positive cytology, bladder mapping was performed and the case was counted as a recurrence only after pathological confirmation of the tumour. Time to recurrence was defined as the time from TUR to the date of the first recurrence.

Progression was defined as an increase in tumour stage and grade. Time to progression was defined as the time between TUR and first progression. Toxicity was assessed on the first day of each cycle with the use of the Common Toxicity Criteria version 3.0 [17]. Grade 3 side effects resulted in patients' exclusion from the study. In the case of grade 2 toxicity, treatment was delayed for 1 week and repeated. If toxicity relapsed at grade 2, treatment was stopped. Side effects were checked after each instillation.

Statistics

The primary endpoint was the recurrence rate. A final target of 20 evaluable patients would provide 80% power to detect an expected recurrence rate of 50%, when using a binomial test with a significance level of 5%. Duration of disease-free interval was estimated according to the Kaplan–Meier method. Descriptive statistics (means, medians and ranges) and the construction of frequency tables were used to analyse patients' baseline clinical characteristics and treatment outcomes. An intention-to-treat analysis was used.

Results

Of 23 initially screened patients with high-risk NMIBC refractory to BCG therapy, 20 were finally enrolled into this trial (Table 1). Seven patients (33%) presented a carcinoma *in situ* (CIS). Median follow-up was 15 months (range 8–21).

Disease recurrence

Complete response rate at the first (3 months) cystoscopy was 75%. Overall, 55% (11 of 20) of patients developed disease recurrence. Only one patient had a positive cytology that was not followed by a biopsy-proven

Table 1 Baseline patient characteristics

	Total = 20
Male/Female	13/7
Mean age (years) ± SD	68.3 ± 5.4
ASA score	
II	4
III–IV	16
Stage	
Ta	4
T1	16
Grade (1998 WHO)	
Low	5
High	15
Number of tumours	
Single	4
2–7	13
≥ 8	3
Tumour diameter (cm)	
<3	8
>3	12
Concomitant CIS	7
Recurrence rate	
Primary	1
≤ 1 per year	5
>1 per year	14
EORTC recurrence score	
10–17	20
EORTC progression score	
7–13	3
14–23	17

ASA, American Society of Anesthesiologists; CIS, carcinoma *in situ;* EORTC, European Organisation for Research and Treatment of Cancer; WHO, World Health Organization.

recurrence. Median time to recurrence was 3.5 months (95% confidence interval 3–6 months). A Kaplan–Meier curve representing 1-year recurrence-free survival is shown in Fig. 1.

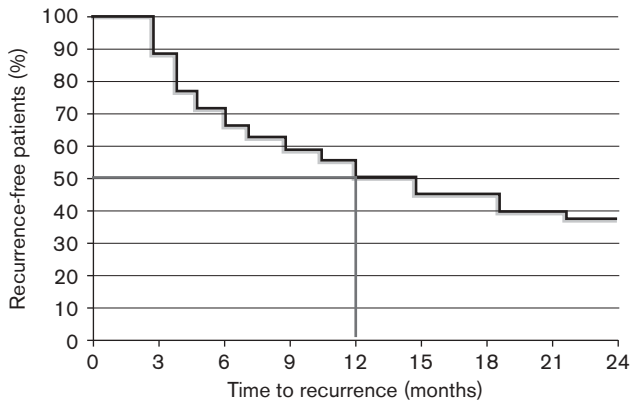
Disease progression

Five of 11 recurring patients (45%) had disease progression (to muscle-invasive disease). Median time to progression was 12.5 months (95% confidence interval 9–14 months). Patients with disease progression were submitted to radical cystectomy (two cases) or radiation therapy plus systemic chemotherapy (three cases). At the time of the last follow-up visit, all patients were alive and disease free. Of the remaining six nonprogressing patients, all underwent radiation therapy plus systemic chemotherapy and were free from disease at the last follow-up visit.

Toxicity

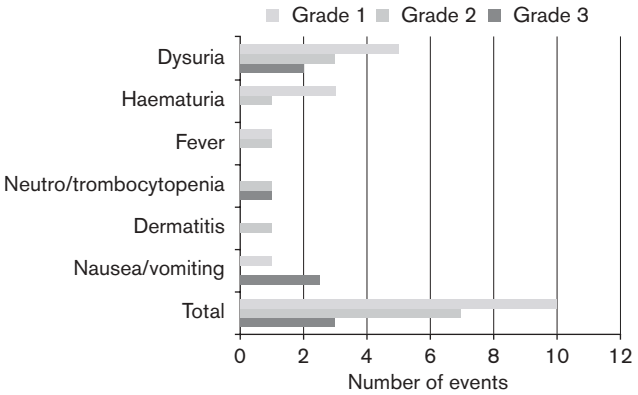
Intravesical administration of gemcitabine was generally well tolerated (Fig. 2). Urinary symptoms represented the main adverse events. They were mostly managed successfully with anticholinergics, antibiotics and/or anti-inflammatory drugs. Overall, few severe (grade 3) adverse events occurred. In two cases, we observed grade 3 dysuria and grade 3 thrombocytopenia in one case. Overall, grade 2 and 3 toxicity rates were 15 and 35%, respectively. According to the protocol, the three patients experiencing grade 3 toxicity were excluded. This was not the case for those experiencing grade 2 toxicity, because none of them experienced another grade 2 event.

Fig. 1



Kaplan–Meier estimation of 1-year recurrence-free survival.

Fig. 2



Toxicity data.

Discussion

The fate of patients failing intravesical therapy and showing progression to muscle-invasive disease is surprisingly bad. Schrier *et al.* [18] found a 3-year bladder-cancer-specific survival of 37% for patients who progressed from superficial to muscle-invasive tumours, compared with 67% for patients with invasive tumours without a history of superficial cancer, after matching tumours for stage and grade. Sylvester *et al.* [5] reported similar findings in a study of BCG-refractory patients with a cancer-specific death rate of 64% at 2.5 year. Huguet *et al.* [6] found that of 62 failures treated with cystectomy, the 5-year disease-specific survival was 38%, significantly lower than that of nonprogressive patients. In summary, the window of opportunity in these patients is limited. This indicates the need for meticulous follow-up, good or repeated TUR and effective treatments in patients in whom BCG fails.

The current recommended treatment option for high-risk BCG-refractory NMIBC is radical cystectomy [9], when patients are willing and compliant. However, this procedure carries a 2–3% mortality rate, and short-term and long-term morbidity occurs in one-third of patients [19].

Although various intravesical regimens have been evaluated in this setting, none of the studies had conclusive findings. One phase II trial addressed the efficacy of bropirimine, an oral immunomodulator, in BCG-resistant CIS of the bladder [20]. Of 47 BCG-resistant evaluable patients, 14 had a complete response. Median response duration was more than 12 months, and only four patients progressed to invasive disease or metastasis. No further evaluation of the drug has been reported so far.

The combination of interferon (IFN)-α and BCG for BCG failures was the subject of a large multicentre phase II trial [21]. Patients received IFN-α plus reduced-dose BCG. All patients who were relapse free received an additional three series of 3-week reduced-dose BCG plus IFN-α treatments at 3, 9 and 15 months after completing induction. Of those with BCG failure, 45% remained disease free at a 24-month median follow-up. Stage T1, tumour size greater than 5 cm, more than one prior BCG failure and multifocality were all statistically significant risk factors for recurrence. On the basis of these findings, the combination of BCG and IFN-α represents a promising second-line regimen after BCG failure, but these results should be confirmed.

Thermochemotherapy has also been reported as being successful in BCG failures [22]. In 41 patients failing BCG treatment, the 1-year and 2-year recurrence rates were 23 and 41%, respectively. Longer follow-up and further results might eventually indicate the value of thermochemotherapy in these patients. Waidelich *et al.* [23] used photodynamic therapy in high-risk BCG-refractory patients, including those with CIS. They found that three of five CIS patients and four of 19 patients with papillary tumours were recurrence free after a median of 36 months.

Valrubicin is the only drug approved by the US Food and Drug Administration for patients with CIS who failed intravesical BCG therapy. This approval was based on a relatively small multi-institutional phase II trial with 90 patients, with a response rate of only 21% and 8% disease-free 2-year survival [24]. More recently, Barlow *et al.* [25] reported their experience with extended intravesical docetaxel for BCG-refractory NMIBC. Thirteen BCG-refractory patients were treated with a 6-week induction, followed by monthly maintenance therapy with intravesical docetaxel for those with a complete response. Ten of the 13 patients had a complete response after induction, and six remained disease free during the 13 months of follow-up.

Attempts have already been made to test the activity of intravesical gemcitabine in high-risk NMIBC (Table 2). In their phase I study, Dalbagni *et al.* [13] treated BCG-refractory patients who refused cystectomy. Four dose levels of gemcitabine were given intravesically for 1 h twice a week. Patients received two courses of six instillations. Only one patient (highest dose level of 2000 mg in 100 ml) experienced grade 3 toxicity. Eleven patients had negative biopsies after treatment, of whom seven also had negative cytology. In their phase II study, the same group treated 30 BCG-refractory patients with biweekly 2000 mg gemcitabine for 3 weeks, with each course separated by 1 week of rest [14]. Complete disappearance of all evidence of disease was obtained in 50% of patients although only 10% were recurrence free at 1 year.

In these reports, complete responses were achieved in series, including a significant proportion of BCG-refractory CIS. In our study population, almost one-third of our patients presented a CIS.

Bartoletti *et al.* [26] administered intravesical gemcitabine in BCG-refractory patients. Eighteen of 24 intermediate-risk and seven of 16 high-risk patients remained recurrence free. Notably, these excellent results in terms of 1-year recurrence-free survival were achieved with a 3-year maintenance schedule identical to the one suggested for BCG.

The same group of investigators reported a small series of selected BCG-resistant T1G3 patients who were unsuitable for radical treatment; these patients were treated with gemcitabine and compared with 10 pT1G3 patients previously treated with further conservative endovesical BCG administration [27]. Of the nine patients treated with gemcitabine, three were recurrence free after 13, 17 and 21 months, and seven kept an intact bladder, with an overall survival rate of 100%. Among the 10 patients treated with BCG instillation, one was recurrence free after 27 months, and six kept their bladders, with a survival rate of 80%.

Finally, Gunelli *et al.* [28] presented a phase II study evaluating the activity of biweekly intravesical gemcitabine. BCG-refractory NMIBC patients received an instillation of 2000 mg on days 1 and 3 for 6 consecutive weeks. Thirty-eight patients (95%) showed persistent negative cystoscopy and cytology at 6 months after treatment. At a median follow-up of 28 months, recurrence had occurred in 14 patients.5

Systemic absorption of intravesical gemcitabine at up to 40 mg/ml, when retained for up to 2 h, is minimal and transient, and is thus unlikely to produce significant adverse events [30]. Overall, no systemic toxicity exceeding grade 2 was recorded in any of the phase I studies, except for one case of grade 3 thrombocytopenia reported by Dalbagni *et al.* [13]. In that case, two factors may have promoted increased systemic absorption: the drug was administered twice a week (as in our experience), and the low pH of the gemcitabine solution could have resulted in an increased nonionic form of the drug that was more likely to pass through the bladder mucosa [31]. Note that in our study no pH adaptation using a buffered solution was performed. Thus, we believe this issue needs to be further addressed.

Table 2 Gemcitabine in BCG-refractory nonmuscle-invasive bladder cancer: data from the literature

Reference	Study type	Pts (*n*)	Schedule	Activity (CR)(%)	Toxicity
[14]	Single-centre phase II	30	2000 mg/100 ml twice weekly for 3 weeks and 1 week of rest	50	Generally well tolerated Grade 3 dysuria in 6 pts
[26]	Multicentre phase II	16	2000 mg/50 ml weekly for 6 weeks	44	Good tolerability and good patient compliance
[27]	Multicentre Comparative nonrandomized	9	2000 mg/50 ml weekly for 6 weeks and then weekly for 3 weeks at 3, 6, 12, 18, and 24 months	33	Only two minor adverse events
[28]	Multicentre phase II	40	2000 mg/50 ml twice weekly for 6 weeks	95	Low urinary and systemic toxicity No alteration in biochemical profile
[29]	Bicentre phase I	9	Three dose levels weekly for 6 weeks	44	No systemic absorption Mild lower urinary tract symptoms

BCG, bacillus Calmette-Guérin; CR, complete response; pts, patients.

Only nine patients with BCG-refractory CIS were enrolled into a phase I study by Bassi *et al.* [29]. Gemcitabine was given once weekly for 6 consecutive weeks at different dose levels. No toxicity of grades 2–4 was observed.

In our trial, gemcitabine was administered with an extensive schedule (twice weekly for 6 weeks). This compared favourably with the 3-week schedule proposed by Dalbagni *et al.* [14].

It has been questioned already whether a more-intensive scheme may be appropriate in selected cases [30]. The major concern was obviously related to the potential toxicity. However, similarly to those of Dalbagni *et al.* [14], our data support the use of such an intensive schedule in terms of toxicity profile. Moreover, we followed the maintenance schedule suggested by Gacci *et al.* [27]. Of course, it is clear that no standard regimen exists in this setting, and the optimal frequency and duration of maintenance instillations remain unknown. Thus, further investigation addressing this issue is needed. We acknowledge the lack of precedent studies with this regimen and the potentially increased systemic absorption and toxicity.

Finally, albeit prospective, our trial suffers from relevant limitations related to the study design. Among them, the small sample size, the lack of a control group and the limited follow-up period did not allow definitive oncological conclusions and limited the applicability of the data.

Our study certainly does contribute to the body of knowledge regarding the treatment of BCG-refractory NMIBC. Of course, a few similar studies have been reported, at least one of which was well conducted, so these findings are not completely novel. The need now is clearly a comparison of gemcitabine to guideline-recommended therapy for this patient population, or a multi-arm comparison study of several regimens.

Conclusion

Findings from this study do not allow us to define the role of gemcitabine as a second-line treatment option in high-risk BCG-refractory NMIBC patients in whom radical cystectomy still represents the first treatment option. Further clinical research in this area is largely awaited.

Acknowledgements

The authors thank Editors for editing this manuscript.

Conflicts of interest: none.

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