Pergamon

European Journal of Cancer, Vol. 34, No. 8, pp. 1208–1212, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(98)00030-6

Original Paper

A Phase II Study of Gemcitabine in Patients with Transitional Cell Carcinoma of the Urinary Tract Previously Treated with Platinum

V. Lorusso,[1] C.F. Pollera,[2] M. Antimi,[3] G. Luporini,[4] C. Gridelli,[5] G.L. Frassineti,[6] C. Oliva,[7] M. Pacini[7] and M. De Lena[1] for the Italian Co-operative Group on Bladder Cancer

[1]Medical Oncology Division, Oncology Hospital, Via Ameridola, 70126 Bari; [2]Medical Oncology Division I, Regina Elena Institute, Rome; [3]Medical Oncology Division, S. Eugenio Hospital, Rome; [4]Medical Oncology Division, S. Carlo Borromeo Hospital, Milan; [5]Medical Oncology Division B, National Cancer Institute, Naples; [6]Medical Oncology Division, Morgagni-Pierantoni Hospital, Forlì; and [7]Eli Lilly Italia, Florence, Italy

The aim of this study was to evaluate the efficacy and safety of gemcitabine, a pyrimidine antimetabolite, in the treatment of advanced transitional cell carcinoma of the urinary tract. 35 patients with unresectable or metastatic transitional cell carcinoma of the urinary tract previously treated with a platinum-based regimen were studied. Gemcitabine was administered at a dosage of 1200 mg/m^2 as a 30-min intravenous infusion on days 1, 8 and 15, repeated every 28 days. 31 patients were evaluable for efficacy. 4 patients achieved a complete response (12.9%), 3 a partial response (9.6%) and 13 (42%) were stable for at least 4 weeks (overall response 22.5%; 95% confidence interval 8–37%). The median response duration was 11.8 months (range 3.6–17.7+ months) and median survival for all patients entered was 5 months (range 2–21+ months). 2 patients with complete response are still alive with no evidence of disease after 14 and 21 months. Gemcitabine also provided subjective symptomatic relief from pain, cystitis, dysuria, haematuria and peripheral oedema. Patients experienced little WHO grade 3–4 toxicity, with anaemia in 8 patients (23%), thrombocytopenia in 5 (14.2%), leucopenia in 4 (11.4%) and neutropenia in 7 (20%). WHO grade 3–4 hepatic toxicity occurred in 4 patients (11.4%) and transient elevations of transaminase was noted in 3 (8.6%). No patient had WHO grade 3–4 elevation of serum creatinine level. There was no WHO grade 4 symptomatic toxicity and no alopecia was noted. Transient influenza symptoms with gemcitabine occurred in 18 patients (51.4%) with 13 patients (37.1%) experiencing fever (2.9% WHO grade 3). In conclusion, gemcitabine is an new active agent for the treatment of transitional cell carcinoma of the urinary bladder with a mild toxicity profile; it warrants further investigation in combination with cisplatin in chemotherapy naive patients.

Key words: gemcitabine, urinary tract carcinoma, treatment outcome, cisplatin pretreated patients
Eur J Cancer, Vol. 34, No. 8, pp. 1208–1212, 1998

INTRODUCTION

GEMCITABINE IS a new pyrimidine antimetabolite with antiblastic activity demonstrated in several solid tumours, such as ovarian, breast, non-small cell lung cancer, pancreatic and bladder cancer [1–7]. It acts by inhibiting ribonucleotide reductase, the enzyme responsible for synthesising deoxynucleotide triphosphates (dCTP) for DNA synthesis, and by competing with dCTP for incorporation into DNA [8]. Moreover, gemcitabine promotes its own activation intracellularly and reduces its clearance from the cell through certain 'self potentiation' mechanisms. Through these

Correspondence to M. De Lena.
Received 3 Sep. 1997; revised 22 Dec. 1997; accepted 23 Jan. 1998.

mechanisms, gemcitabine remains within the tumour cells at higher levels for longer periods of time, and exhibits a broader activity against solid tumours as compared with the structurally similar aracytin (ara-C) [9, 10].

With regard to dose schedules, phase I studies have demonstrated that a daily schedule was not possible because of severe influenza-like symptoms and considerable hypotension in some patients [11]. The twice-weekly schedule and the alternating weekly schedule were also tested, but rapidly abandoned because of severe thrombocytopenia and poor efficacy, respectively [12, 13]. A weekly schedule (gemcitabine administered once-weekly for 3 weeks followed by a 1 week interval), however, seemed to provide a combination of activity and acceptable tolerability, with thrombocytopenia (maximum tolerated dose: 790 mg/m^2 in previously treated patients) as the dose-limiting toxicity. In fact, this schedule at a dosage of more than 875 mg/m^2 once-weekly for 3 weeks followed by a 1 week interval showed significant antitumoral activity (21.4% overall response) in a phase I study [6] in 14 patients with bladder cancer refractory to M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin). Moreover, toxicity was mild and easily manageable at dosages of less than 1370 mg/m^2/week.

On the basis of these data, we designed a phase II multiinstitutional study of gemcitabine in patients with advanced transitional cell carcinoma of the urinary tract who had received one prior cisplatin-based chemotherapeutic regimen to determine the objective response rate to gemcitabine. The secondary aims of the study were to determine the response duration and survival time, and to characterise further the toxicity profile of gemcitabine in this group of patients.

PATIENTS AND METHODS

Patient characteristics

From January 1993 to January 1995, 35 patients with inoperable or metastatic transitional cell carcinoma of the urinary tract who had previously received a platinum-based regimen were included in this multicentre, open-label nonrandomised phase II trial. The baseline characteristics of the patient population are reported in Table 1. The most frequent sites of distant metastases were: lung (5 patients), liver (8 patients), pelvic masses (20 patients), soft tissue/skin or lymph nodes (18 patients), bone (1 patient). 29 patients (83%) had previously been submitted to radical cystectomy and adjuvant radiation therapy to the pelvis had been applied to 10 patients (29%) just after surgery. 29 of 35 patients had received one previous cisplatin-based chemotherapy for advanced disease (usually M-VAC or M-VAC-like), whereas 6 patients had received a cisplatin-based regimen as adjuvant treatment, after complete removal of primary cancer and in the absence of distance metastases.

Table 1. *Patient characteristics*

Characteristic	*n*	%
Entered	35	100
Evaluable	31*	89
Median age (years) (range)	64 (38–74)	
Male:Female	29:6	
ECOG performance status		
3	1	3
2	20	57
0–1	14	40
Previous radical cystectomy	29	83
Previous cisplatin therapy	35	100
Previous radiotherapy	10	29

*4 patients not evaluable (heart failure, increase of bilirubinaemia pneumonia and refusal before completing first cycle).

Eligibility criteria included the presence of bidimensionally measurable lesions over 2 cm in size, as assessed by X-rays, computed tomography scan, physical examination or other diagnostic techniques, as appropriate; life expectancy of at least 12 weeks; completion of other forms of therapy, such as high dose steroids at least 3 weeks before entering study; adequate bone marrow reserve defined as a white blood cell count of 4×10^9/l or greater (neutrophils $>1500\times10^9$/l, platelets $\geq 100\times10^9$/l, haemoglobin ≥ 10 g/dl); adequate renal (creatinine ≤ 1.5 mg/dl) and liver function (bilirubin ≤ 3 mg/dl; AST/ALT $\leq 111/120$ U/l). Patients were excluded in the presence of current or previous central nervous system metastases, secondary malignancies (except *in situ* carcinoma of the cervix or adequately treated basal cell carcinoma of the skin). Other exclusion criteria included pregnancy, breast feeding, acute serious infection, active uncontrolled hypercalcaemia, significant neurological (i.e. seizures) or psychiatric disorders and serious concomitant systemic disorders incompatible with the study at the discretion of the investigator. The protocol was approved by the Ethics Committee of each participating institution and a signed informed consent was obtained from all screened patients.

Treatment

Treatment was on an out-patient basis. Gemcitabine, kindly supplied by Eli-Lilly Indianapolis, U.S.A., was administered at a dosage of 1200 mg/m^2 intravenously over 30 min on days 1, 8 and 15 of a 28-day cycle. As an anti-emetic, ondansetron, 8 mg intravenously, was administered just prior to gemcitabine. Treatment was carried out for a maximum of eight cycles in responding patients or patients with stable disease and was discontinued in the presence of disease progression or severe toxicity. A detailed medical interview, clinical examination and laboratory studies were obtained before each drug administration. Dose adjustments were based on assessment of haematological and non-haematological toxicity. In particular, only 75% of the gemcitabine dose was administered when granulocytes measured 1.0–1.4×10^9/l and/or platelets 75–99.9×10^9/l. If granulocytes were 0.5–0.9×10^9/l and/or platelets 50–74.9×10^9/l, 50% of the full dose was administered. If the cell counts fell below the lower level of either ranges, the treatment was delayed until recovery. Patients with grade 3 non-haematological toxicity had a 50% dose reduction. Patients with life-threatening grade 4 non-haematological toxicity were withdrawn from the study. No other chemotherapy, hormonal therapy or experimental medications was permitted while the patients were in the study. Patients with disease progression discontinued gemcitabine and were administered alternative specific antitumour therapy. Irradiation therapy of painful lesions was permitted provided that at least another measurable lesion was present outside the field of irradiation.

Evaluation of response and toxicity

All patients who completed at least one therapy cycle (three injections and a tumour reassessment after a 1-week interval) were analysed for chemotherapeutic efficacy. All enrolled patients were analysed for toxicity and survival and were

reviewed at every monthly visit to assess efficacy and toxicity. After discontinuation of treatment, patients were evaluated every 3 months to assess survival and disease-free status. The evaluation of tumour response was based on the standard WHO criteria for measurable disease [14].

For evaluation of tumour response and survival, the following definitions were used: time to response, time from first injection to first objective response; time to progression, time from first injection to date of evidence of progression; time to treatment failure, time from first injection to date of withdrawal from the study for any reason (progression, toxicity, refusal, lost to follow-up); duration of response, time from first injection to time of progression for partial responses; for complete responses, time from first evidence of complete response to time of disease progression; survival, time from first injection to death or last follow-up visit.

Methods to evaluate efficacy included the tumour response rate both by 'standard analysis' which considers only patients completing at least one cycle of therapy and whose tumour reassessment is performed after a 1-week interval, and by 'intent to treat' analysis which considers all patients entered in the study as evaluable, thus viewing withdrawn patients for any cause as treatment failure. The Kaplan–Meier analysis was used for analyses of survival and time to progression or time to treatment failure; 95% confidence intervals (CI) were also calculated.

RESULTS

A total of 31 of 35 patients received at least three doses of gemcitabine and qualified for efficacy analysis; 4 patients were not evaluable because of three early non-gemcitabine-related adverse events (heart failure, rapid increase of bilirubinaemia, pneumonia), and 1 refusal for personal reasons. Of the 31 evaluable patients, 4 achieved a complete response (12.9%) and 3 a partial response (9.6%), with an overall response rate of 22.5% (95% CI 8–37%). The response rate calculated on an intent to treat basis was 20%. 13 patients had stable disease. Of the 7 responding patients, lung or liver metastases were observed as the dominant site of disease in 2 patients, pelvic masses in 2 patients, lumbo-aortic or supraclavicular nodes in 2 patients, and bone metastases in 1 patient. Moreover, 1 patient with pelvic and lumbo-aortic lymph nodes disease sites who achieved a partial response, also demonstrated destruction of large urethral and vessical papillary tumours with recalcification of an osteolytic bone lesion. However, tumour regression in this patient lasted only 3.6 months (Table 2).

With regard to previous response to cisplatin-based chemotherapy, it is noteworthy that one of the responding patients had progressed on M-VAC, whereas 4 patients responding to gemcitabine had previously responded to M-VAC but subsequently relapsed (6–12 months after M-VAC discontinuation). Moreover, for 2 responding patients, data on previous response to chemotherapy were not available because these patients had received M-VAC as adjuvant treatment 13 and 48 months before, respectively (Table 2). With regard to the 24 patients not responding to gemcitabine, it is noteworthy that only 3 of 24 (12.5%) had previously responded to M-VAC or M-VAC-like regimens and in 4 of 24 (17%), the previous response to M-VAC could not be assessed because of the adjuvant setting.

The overall median time to response was 1.6 months; the median duration of response was 11.8 months (range 3.6–17.7^+ months) and the median time to progression was 3.8 months. The median survival for all 35 patients was 5 months (range 2–21^+ months). 2 patients with complete response are still alive with no evidence of disease after 14 and 21 months. With regard to assessment of symptom amelioration, of the 29 patients complaining of pain at the start of treatment, 12 (41%) improved. Also, some disease-related symptoms, such as cystitis, dysuria and peripheral oedema, also showed a marked improvement with therapy. A total of 304 doses of gemcitabine were administered: 75% were administered as scheduled, 22% were reduced and 3% omitted. The mean dose delivered per injection was 1104 mg/m^2 and the mean number of completed cycles was 2.7.

Toxicity

The treatment was generally well tolerated (Table 3). Grade 3–4 leucocyte toxicity was recorded in only 3 (8.6%) and 1 (2.9%) patients, respectively, and grade 3–4 neutropenia was observed in 4 (11.4%) and 3 (8.6%) patients, respectively. Grade 3–4 thrombocytopenia was observed in 2 (5.7%) and 3 (8.6%) patients, respectively. Anaemia (grade 3–4) was seen in 8 patients. Moreover, the incidence of infections related to neutropenia was low, with no WHO grade 3–4 infections. 2 patients required hospitalisation for grade 4 thrombocytopenia and grade 4 anaemia, respectively. WHO grade 3–4 biochemical toxicity of AST/ALT, ALP or bilirubin occurred in 4 patients (11.4%), and transient elevations of AST, ALT and ALP were observed in 3 (8.6%), 2 (5.7%) and 3 (8.6%) patients, respectively. 1 patient with grade 4 ALT toxicity was withdrawn from study after the third cycle. Alterations in other liver enzymes were mild and

Table 2. Characteristics of 7 patients responding to gemcitabine

Response	Disease site	Previous response to M-VAC	Chemotherapy-free interval (months)*	Time to response (months)	Time to complete response (months)	Response duration (months)	Survival (months)
CR	Lung + pelvis	CR	12	1.3	1.3	12.7+	14+
CR	Lymph nodes	PR	6	1.6	7	11.8	18.9+
CR	Lymph nodes	CR	7	2.6	5.7	15.8+	21+
CR	Pelvis	n.a.	48	2	2	17.7	19.8
PR	Lung + liver	PD	1.5	1	–	11.8	12.3
PR	Pelvis	n.a.	13	1.2	–	6.8	14.9
PR	Pelvis + bone + lymph nodes	PR	6	1.9	–	3.6	6.2

CR, complete response; PR, partial response; PD, progressive disease; n.a., not available; M-VAC, methotrexate, vinblastine, doxorubicin, and cisplatin.

*Time elapsed from last M-VAC administration and first administration of gemcitabine.

Table 3. Maximum WHO grades for symptomatic toxicity (%)

Toxicity	0	1	2	3	4
Allergy	97.0	0.0	0.0	2.9	0.0
Constipation	85.7	11.4	0.0	2.9	0.0
Cutaneous	88.6	5.7	5.7	0.0	0.0
Diarrhoea	94.3	2.9	2.9	0.0	0.0
Influenza-like	48.6	17.1	31.4	2.9	0.0
Fever	63.0	14.2	20.0	2.9	0.0
Cardiac	100.0	0.0	0.0	0.0	0.0
Alopecia	100.0	0.0	0.0	0.0	0.0
Infection	97.1	2.9	0.0	0.0	0.0
Nausea/vomiting	48.6	14.3	20.0	5.7	0.0
Oral	88.5	8.6	2.9	0.0	0.0
Pulmonary	97.1	0.0	0.0	2.9	0.0

without clinical significance. No patient had WHO grade 3–4 elevation of serum creatinine level or BUN.

With regard to symptomatic toxicity, nausea and vomiting were generally modest (5.7% WHO grade 3) and no alopecia was reported in 30 of 35 patients in which this side-effect could be assessed because of no pre-existing alopecia due to a previous M-VAC. Transient influenza-like symptoms were associated with gemcitabine in 18 patients (51.4%) with 13 patients (37.1%) experiencing fever (2.9% with WHO grade 3). 1 patient (2.9%) experienced a WHO grade 3 allergic reaction (dyspnoea and cutaneous rash) which was successfully treated with steroids and aminophylline. 1 patient (2.9%) reported grade 3 constipation, and another patient (2.9%) complained of dyspnoea and moderate to severe respiratory distress 2 h after gemcitabine administration. However, the initial entry visit of this patient had revealed an underlying obstructive pneumopathy. In addition, 3 patients were withdrawn from the study before completing the first cycle of therapy due to adverse events: heart failure, pneumonia and relevant bilirubin increase, respectively. However, all these adverse events were considered as possibly non-gemcitabine-related because of previous history of cardiopathy in the first patient, an underlying pulmonary infection in the second patient and the presence of massive liver involvement in the third patient.

DISCUSSION

Transitional cell carcinoma of the urothelium is a chemosensitive tumour as demonstrated by the overall response rate of 35–70% with the M-VAC drug combination [15, 16]. However, the toxicity of this regimen is significant and the median survival of all treated patients does not greatly exceed 12 months [17, 18]. These results have prompted a search for new active agents which could be incorporated into more effective and less toxic regimens. The chemotherapy agents that have shown activity in metastatic bladder cancer are ifosfamide, gallium nitrate, paclitaxel and gemcitabine [6, 19–21]. However, ifosfamide and gallium nitrate have shown limited activity in patients previously treated with cisplatin, and their toxicity is usually more relevant than that of gemcitabine [19, 20] and the activity of paclitaxel needs to be confirmed in further studies [21].

In the present study of 31 previously platinum-treated evaluable patients with advanced transitional cell cancer of the urinary tract, gemcitabine administered at a dosage of 1200 mg/m^2 week for 3 weeks every 28 days showed significant activity, with an objective response rate of 22.5%. Moreover, responses were observed in pelvic masses, lung, liver, lymph nodes and bone lesions, suggesting that gemcitabine may have significant activity in sites which only seldomly respond to M-VAC, such as liver and bones [22]. Even though the survival of these patients was only slightly improved as compared with that reported in patients relapsing after cisplatin-based chemotherapy and treated with supportive care only [18], the 22.5% objective response rate with this single agent is encouraging and suggests the possibility of a higher activity in non-treated patients. In fact, in two recent phase II studies on untreated patients with transitional cell carcinoma of the urinary tract, gemcitabine had significant activity and a favourable toxicity profile [23, 24]. In the first study, 5 of 9 (56%) untreated patients responded to gemcitabine administered at a dosage of 1200 mg/m^2 weekly for 3 of 4 weeks [23]. In the second study, a Canadian multi-institutional trial [24], also performed on previously untreated patients, 8 of 21 patients responded (38%; 95% CI 18–62%).

In conclusion, the 22.5% response rate seen in this study confirms gemcitabine as an active effective single agent in transitional cell carcinoma of the urinary tract. The activity of gemcitabine together with its mode of action, modest toxicity, and non-overlapping side-effects with cisplatin, supports the investigation of this drug in chemotherapeutic combinations for treatment of advanced bladder cancer and strongly suggests that gemcitabine can now be included in new regimens in large co-operative phase III trials to compare the efficacy of this chemotherapy with the standard M-VAC treatment.

1. Hertel LW, Boder GB, Kroin JS, *et al.* Evaluation of the antitumor activity of gemcitabine (difluor-2′-deoxy-citidine). *Cancer Res* 1990, **50**, 4417–4422.
2. Abbruzzese JL, Grunewald R, Weeks EA, *et al.* A phase I clinical, plasma and cellular pharmacology study of gemcitabine. *J Clin Oncol* 1991, **9**, 491–498.
3. Gatzeimer U, Shepherd FA, Le Chevalier T, *et al.* Activity of gemcitabine in patients with non-small cell lung cancer: a multicentre, extended phase II study. *Eur J Cancer* 1996, **32A**, 243–248.
4. Lund B, Hansen OP, Theilade K, Hansen M, Neijt JP. Phase II study of gemcitabine in previously treated ovarian cancer patients. *J Natl Cancer Inst* 1994, **86**, 1530–1533.
5. Carmichael J, Passinger K, Philip P, *et al.* Advanced breast cancer: a phase II trial with gemcitabine. *J Clin Oncol* 1995, **13**(11), 2731–2736.
6. Pollera CF, Ceribelli A, Crecco M, Calabresi F. Weekly gemcitabine in advanced bladder cancer: a preliminary report from a phase I study. *Ann Oncol* 1994, **5**, 182–184.
7. Carmichael J, Fink U, Russel RCJ, *et al.* Phase III study of gemcitabine in patients with advanced pancreatic cancer. *Br J Cancer* 1996, **73**, 101–105.
8. Huang P, Chung S, Hertel LW, Grindey JB, Plunkett W. Action of 2′,2′-difluorodeoxycytidine on DNA synthesis. *Cancer Res* 1991, **51**, 6110–6117.
9. Heinemann V, Hertel LW, Grindey GB, *et al.* Comparison of the cellular pharmacokinetics and toxicity of 2′-2′-difluorodeoxycytidine and 1-D-arabinofuranosylcytosine. *Cancer Res* 1988, **48**, 4024–4031.
10. Heinemann V, Xu YZ, Chubb S, *et al.* Cellular elimination of 2′,2′-difluorodeoxycytidine 5′-triphosphate: a mechanism of self-potentiation. *Cancer Res* 1992, **52**, 533–539.
11. O'Rourke TJ, Brown TD, Havlin K, *et al.* Phase I clinical trial of gemcitabine as an intravenous bolus for 5 consecutive days. *Eur J Cancer* 1994, **30**, 417–418.
12. Poplin E, Corbett T, Flaherty L, *et al.* Difluorodeoxycytidine (dFdC)–gemcitabine: a phase I study. *Inv New Dr* 1992, **10**, 165–170.

13. Tanis B, Clavel M, Guastalla J, *et al.* Phase I study of gemcitabine (difluorodeoxycytidine dFdC (LY188011)) administered in a two weekly schedule. *Proc Am Assoc Cancer Res* 1990, **31**, 1239.
14. WHO Handbook for Reporting Results of Cancer Treatment. Geneva, World Health Organisation, 1979.
15. Stenberg CN, Yagoda A, Sher HI, *et al.* Methotrexate, vinblastine, doxorubicin and cisplatin for advanced transitional cell carcinoma of the urothelium. *Cancer* 1989, **64**, 2448–2458.
16. Roth BJ. Palliative chemotherapy in advanced bladder cancer. *Semin Oncol* 1995, **22**(Suppl. 3), 10–15.
17. Tannock I, Gospodarowicz M, Connolly J, *et al.* M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) chemotherapy for transitional cell carcinoma: The Princess Margaret Hospital experience. *J Urol* 1989, **142**, 289–292.
18. Dismopulos MA, Finn L, Logothetis CJ, *et al.* Pattern of failure and survival of patients with metastatic urothelial tumours relapsing after cisplatin based chemotherapy. *J Urol* 1994, **151**, 598–601.
19. Witte RS, Elson P, Bono B, *et al.* Eastern Co-operative Oncology Group phase II trial of ifosfamide in the treatment of previously treated advanced urothelial carcinoma. *J Clin Oncol* 1997, **15**, 589–593.
20. Einhorn LM, Roth BJ, Ansari R, *et al.* Phase II trial of vinblastine, ifosfamide and gallium combination chemotherapy in metastatic urothelial carcinoma. *J Clin Oncol* 1994, **12**, 2271–2276.
21. Roth BJ. Preliminary experience with paclitaxel in advanced bladder cancer. *Semin Oncol* 1995, **22**(3 Suppl. 6), 1–5.
22. Igawa M, Ohkuchi T, Ueki T, *et al.* Usefulness and limitations of methotrexate, vinblastine, doxorubicin and cisplatin for the treatment of advanced urothelial cancer. *J Urol* 1990, **144**, 662–665.
23. Stadler W, Kuzel T, Raghavan D, Levine, E, Vogelzang N, Dorr A. A phase II study of gemcitabine in the treatment of patients with advanced transitional cell carcinoma. *Proc Am Soc Clin Oncol* 1995, **14**, 241 (abstract 638).
24. Moore MJ, Tannock I, Ernst S, Huan S, Murray N. Gemcitabine demonstrates promising activity as a single agent in the treatment of metastatic transitional cell carcinoma. *Proc Am Soc Clin Oncol* 1996, **15**, 250 (abstract 637).

Acknowledgements—The authors are grateful to Ms Paulene Maselli Campagna for her assistance in the preparation of the manuscript.