Gemcitabine and ifosfamide as a second-line treatment for cisplatin-refractory metastatic urothelial carcinoma: a phase II study

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Few treatment options are available for cisplatin-refractory urothelial carcinoma. We evaluated the efficacy and safety of a new regimen composed of gemcitabine and ifosfamide as a second-line salvage chemotherapy for the disease. The gemcitabine and ifosfamide regimen consists of gemcitabine 800 mg/m^2/day intravenously for 30 min on days 1, 8, and 15; ifosfamide 1500 mg/m^2/day intravenously for 24 h on days 8–10; and mesna 800 mg intravenously bolus before ifosfamide and 1500 mg/m^2/day intravenously for 24 h on days 8–11. Cycles are repeated every 28 days. Between 1998 and 2005, 23 patients (median age 66) unresponsive to cisplatin-based chemotherapy ($n=10$) or who had tumor progression within 6 months of a previous response to cisplatin-based therapy ($n=13$) were enrolled. The median interval between the two chemotherapy regimens was 1.8 months (range 0.9–5.6). In total, 82 treatment cycles (median 3, range 1–8) were given. The overall response rate was 22% (95% confidence interval 5–39) with one complete response and four partial responses. Twenty-one patients succumbed to the disease. The median progression-free survival and overall survival were 3.5 and 4.8 months, respectively. Grade 3 or 4 leukopenia and thrombocytopenia occurred in 10 and eight patients, respectively. One, two and two patients complicated with grade 3 vomiting, diarrhea and stomatitis were present, respectively. No grade 3 or 4 neurotoxicity or nephrotoxicity was seen in these patients. The gemcitabine and ifosfamide regimen has an acceptable toxicity profile, but shows insufficient clinical activity in patients with cisplatin-refractory urothelial carcinoma to warrant further testing. *Anti-Cancer Drugs* 18:487–491 © 2007 Lippincott Williams & Wilkins.

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Introduction

No standard salvage regimens are available for the treatment of cisplatin-refractory metastatic urothelial carcinoma (UC). Patients usually die of the refractory disease in 2–3 months if left untreated [1].

Gemcitabine is a pyrimidine antimetabolite, which inhibits ribonucleotide reductase and DNA synthesis [2]. Toxicity is usually self-limiting, with mild leukopenia, fever and skin rash being the most common reported. In four studies, with 131 UC patients, which evaluated the efficacy of the single agent gemcitabine, the objective response rate was 23–28% with 7–13% having a complete response (CR). The median overall survival was 5–12 months [3–6]. The response rate was similar between cisplatin-pretreated [3,6] and chemonaive patients [4,5].

Ifosfamide was shown to be an active agent for cisplatin-pretreated metastatic UC. In an Eastern Cooperative Oncology Group Case II study, ifosfamide (3750 mg/m^2/day for 2 days or 1500 mg/m^2/day for 5 days, repeated every 21 days) achieved an objective response rate of 21% with five CRs. The toxicity was, however, significant, including severe bone marrow, renal, central nervous system and gastrointestinal toxicity [7], suggesting that the dosing schedule of ifosfamide would have to be modified to avoid excessive toxicity.

Gemcitabine and ifosfamide (GI) are active against cisplatin-pretreated metastatic UC, act through different mechanisms and do not have overlapping toxicity. As a result of the widespread use of cisplatin and 5-fluorouracil, with or without paclitaxel as the first-line treatment at our institution [8,9], most patients with cisplatin-refractory metastatic UC are gemcitabine-naive. Therefore, we conducted a phase II clinical study combining GI for the treatment of cisplatin-refractory metastatic UC.

Patients and methods

The protocol was reviewed and approved by the Research Ethics Committee of National Taiwan University Hospital. All patients provided written informed consent before enrollment. Patients were recruited between December 1998 and December 2005, and were followed up until 15 August 2006.

Eligibility criteria

Patients who were over 18 years old with pathologically verified UC and previously treated with cisplatin-based chemotherapy for metastatic disease were enrolled. The patients' Karnofsky performance status should be 50% or better. All patients had only one prior chemotherapy treatment. All patients did not respond to first-line cisplatin-based regimens or experienced disease progression within 6 months of the last cycle of cisplatin-based therapy. A minimum of 4 weeks existed between the end of any previous chemotherapy and the initiation of the described GI protocol. Patients must have had a creatinine clearance of ≥ 30 ml/min, a total bilirubin ≤ 2 mg/dl and liver transaminases ≤ 3.5 times the upper normal limit. All patients had at least one bidimensionally measurable lesion sized 1×1 cm or greater revealed by radiographic examinations.

Treatment plan

The GI regimen consisted of gemcitabine 800 mg/m^2/day as a 30-min intravenous infusion on days 1, 8 and 15; ifosfamide 1500 mg/m^2/day as a 24-h continuous intravenous infusion on days 8–10; and mesna 800 mg intravenous bolus injection before ifosfamide, then mesna 1500 mg/m^2/day as a 24-h continuous intravenous infusion on days 8–11. The treatment cycles were repeated every 28 days. Criteria for any next cycle of treatment included a white blood cell count $\geq 3000/\mu$l, a platelet count $\geq 100\,000/\mu$l and the absence of $\geq$ grade 2 nonhematologic toxicities except alopecia. Granulocyte colony-stimulating factor was not routinely used.

Dose modification plan

The dose of ifosfamide was reduced to 1000 mg/m^2/day on days 8–10 if the patient had an Eastern Cooperative Oncology Group (ECOG) grade 4 leukopenia, neutropenia or thrombocytopenia during the previous cycle, or if the scheduled treatment had to be delayed for 1–2 weeks. Ifosfamide was not administered if such a dose modification or schedule delay did not prevent the occurrence of grade 4 myelosuppression. The dose of ifosfamide was reduced to 1000 mg/m^2/day if the serum creatinine was ≥ 2 mg/dl or creatinine clearance was < 30 ml/min. When microscopic hematuria occurred, as determined to be $\geq 2+$ employing urine dipsticks, ifosfamide was discontinued until the hematuria was resolved.

Evaluation of tumor response and toxicity

Response was evaluated by computed tomography at the end of every two cycles using the standard World Health Organization criteria [10]. The protocol treatment would be discontinued permanently for documentation of progressive disease. For patients with a CR or partial response (PR), treatment would be continued for two more cycles after the maximal tumor response was reached. If there was a stable disease after four cycles of treatment, patients could be continued on or off the protocol treatment at the discretion of responsible physicians. Complete blood cell count with white blood cell differentiation was checked on days 1, 8 and 15 of each cycle. Blood biochemistry and electrolytes were monitored at the beginning of each cycle. Toxicity was evaluated every week using the ECOG toxicity criteria [11].

Statistics

The primary objective of this study was to determine the response rate of the combination regimen. The secondary objectives were to document treatment-related toxicity, progression-free survival and overall survival. The study was designed to test 23 patients so that the lower 95% confidence limit (CI) was higher than the hypothesized null response rate of 10%, provided that the true response rate was $\geq 30\%$. The regimen would be rejected if an objective response was seen in six or less of 23 patients. This design provided a statistical power of 90%.

Progression-free survival was defined as the duration from the date of starting the protocol treatment to the date of documented disease progression, death due to any causes (censored) or last follow-up (censored). Overall survival was calculated from the date of starting the protocol treatment to the date of patient death or last follow-up (censored). Both the progression-free survival and overall survival were calculated by using the Kaplan–Meier method. The associations between objective responses and various clinical parameters were evaluated using the χ^2 or Fisher's exact test. The log-rank test was used to compare the impact of various clinical parameters on survival.

Results

Patient characteristics

Twenty-three patients, 17 men and six women, were recruited for this study. Demographic and tumor features are summarized in Table 1. The median age was 66 years (range 40–76). Ten patients were unresponsive to previous cisplatin-based chemotherapy. Thirteen patients had progressed within 6 months of the cisplatin-based chemotherapy. Among them, four patients had received the CMV-T regimen (cisplatin 50 mg/m^2 2-h intravenously on days 1 and 2; methotrexate 30 mg/m^2 intravenously on days 1, 8; vinblastine 3 mg/m^2 intravenously on days 1, 8; tamoxifen 200 mg/m^2/day orally on

Table 1 Patient characteristics ($n=23$)

	n	%
Karnofsky performance status (%)		
90	1	4
80	14	61
70	8	35
Primary site		
Renal pelvis	7	30
Ureter	3	13
Bladder	12	52
Urethra	1	4
Metastatic site		
Visceral		
Liver	3	13
Lung	3	13
Bone	5	22
Liver and bone	6	26
Lung, liver, and bone	1	4
Nonvisceral		
Lymph nodes only	4	17
Soft tissue only	1	4
Prior chemotherapy		
CMV-T	4	17
P-HDFL	6	26
TP-HDFL	13	57
Response to prior chemotherapy		
Partial response	13	57
Stable disease	4	17
Progressive disease	6	26
Total	23	100

CMV-T, cisplatin, methotrexate, vinblastine, and high-dose tamoxifen [12]; P-HDFL, cisplatin and high-dose 5-fluorouracil plus leucovorin [8]; TP-HDFL, paclitaxel, cisplatin, and high-dose 5-fluorouracil plus leucovorin [9].

days 1–4; repeated every 21 days) [12], six patients had received the P-HDFL regimen (cisplatin 35 mg/m^2 24-h intravenously on days 1, 8; 5-fluorouracil 2600 mg/m^2 and leucovorin 300 mg/m^2 24-h intravenously on days 1, 8, 15; repeated every 28 days) [8] and 13 patients had received the TP-HDFL regimen (paclitaxel 70 mg/m^2 1-h intravenously on days 1, 8; cisplatin 35 mg/m^2 24-h intravenously on days 2 and 9; 5-fluorouracil 2000 mg/m^2, and leucovorin 300 mg/m^2 24-h intravenously on days 2 and 9; repeated every 21 days) [9] as their first-line chemotherapy. None of the previous chemotherapies were in an adjuvant or neoadjuvant setting. The treatment-free interval was 1.8 months (range 0.9–5.6) (Table 1).

Dose modification

Dose modifications were made in 11 patients (48%) or 24 cycles (29%). The actual dosages of GI administered to these patients were 93 (range 67–100) and 87% (range 50–100) of planned dosages, respectively.

Toxicity

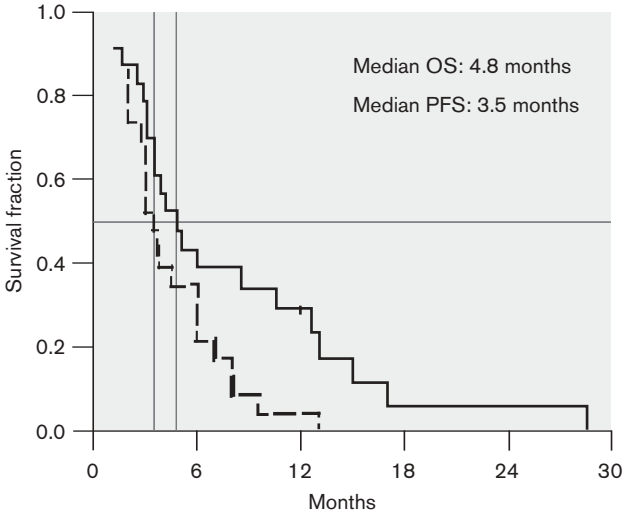
Among the total of 23 patients, grade 3 or 4 leukopenia, anemia and thrombocytopenia occurred in 10, five and eight patients, respectively. Two, one, two and two patients experienced grade 3 but no grade 4 nausea, vomiting, stomatitis, and diarrhea, respectively. No grade 3 or 4 nephrotoxicity or neurotoxicity was seen in our patients (Table 2).

Table 2 Toxicity profile ($n=23$)

	ECOG toxicity grades (cycles)			
	1	2	3	4
Hematological				
Anemia	5 (22)	10 (43)	3 (13)	2 (9)
Leukopenia	4 (17)	5 (22)	6 (26)	4 (17)
Thrombocytopenia	4 (17)	2 (9)	5 (22)	3 (13)
Nonhematological				
Infection	4 (17)	2 (9)	1 (4)	2 (9)
Nausea	7 (30)	3 (13)	2 (9)	–
Vomiting	6 (26)	3 (13)	1 (4)	0
Diarrhea	2 (9)	1 (4)	2 (9)	0
Alopecia	4 (17)	7 (30)	–	–
Stomatitis	3 (13)	2 (9)	2 (9)	0
Hepatic toxicity	5 (22)	3 (13)	1 (4)	1 (4)
Renal toxicity	5 (22)	4 (17)	0	0
Neurotoxicity	3 (13)	0	0	0
Skin toxicity	3 (13)	1 (4)	0	0

ECOG, Eastern Cooperative Oncology Group.

Fig. 1



Overall survival (OS) (solid line) and progression-free survival (PFS) (dashed line) curve ($n=23$).

Response and survival

A total of 82 cycles were given with a median of three cycles/patient (range 1–8). All 23 patients were eligible for response evaluation. One CR, four PRs, 10 stable diseases and five progressive diseases were present. The intent-to-treat objective response rate was 22% (95% CI, 5–39%). The median duration of response was 6.0 months (range 3.0–13.0). Objective responses were seen in two of the 10 patients who had failed the first-line cisplatin-based regimens. Eighteen patients had visceral metastasis (liver, lung and/or bone). One patient with liver metastase (6%) achieved a CR. One patient with bone and liver metastase and one patient with bone and lymph node metastases (11%) achieved a PR.

The median progression-free survival and overall survival of these 23 patients were 3.5 (95% CI, 2.8–4.2) and 4.8 months (95% CI, 2.9–6.6), respectively (Fig. 1).

Table 3 Two-drug combination chemotherapy for cisplatin-pretreated metastatic urothelial carcinoma

Regimen	Patients	TFI (months)	Visceral mets (%)	RR (%)	CR (%)	OS (months)
Gemcitabine, lonafarnib [20]	33	5.3 (0.9–88)	NR	30	3	11.5
Oxaliplatin, fluorouracil [21]	16	NR	NR	19	0	4.0
Paclitaxel, carboplatin [22]	44	5	64	16	2	6.0
Paclitaxel, ifosfamide [23]	13	NR	NR	15	15	8.0
Docetaxel, ifosfamide [24]	22	6 (1–100)	64	25	20	4.0
Gemcitabine, ifosfamide [25]	34	4 (0.4–32)	NR	21	3	9.0
Gemcitabine, ifosfamide (this study)	23	1.8 (0.9–5.6)	78	22	4	4.8

CR, complete response; NR, not reported; OS, overall survival; RR, response rate; TFI, treatment-free interval.

Discussion

Cisplatin-refractory UC has been a difficult condition for both urologists and oncologists to treat. In addition to GI, a number of cytotoxic agents have been tested in the second-line setting with varying degrees of efficacy. The taxanes are frequently used in clinical practice, because they yielded an objective response rate of 7–13% with a response duration between 3.0 and 7.4 months. Common side effects are severe myelosuppression with docetaxel and peripheral neuropathy with paclitaxel [13–15]. Recent trials with oxaliplatin (a novel platinum analog) [16], lonafarnib (a farnesyl transferase inhibitor) [17], lapatinib (a dual targeted tyrosine kinase inhibitor) [18] and bortezomib (a proteosome inhibitor) [19] have shown unimpressive results.

A variety of two-drug combinations have been tested for the treatment of cisplatin-refractory UC (Table 3) [20–25]. The combination of paclitaxel and ifosfamide was tested in a phase II study of 13 patients who had previously received a platinum-based chemotherapy. The response rate was 15% with CR in two patients [23]. Docetaxel and ifosfamide was tested in 22 patients, with a response rate of 25% with CR in four patients [24]. A GI combination was tested in a second-line setting, and a similar response rate of 21% was obtained among 34 platinum and/or taxane pretreated patients with advanced UC. A relevant observation was that symptomatic improvements were achieved in a significant number of patients [25]. Gemcitabine has also been studied in combination with lonafarnib in the second-line setting. Nine PRs and one CR were achieved among the 31 assessable patients; this corresponded to an overall response rate of 32% [20]. Di Lorenzo *et al.* [21] examined the combination of oxaliplatin and fluorouracil with folinic acid (FOLFOX-4) in 16 pretreated patients with an overall response rate of 19%.

The most promising approach for a second-line regimen is introducing novel agents, such as pemetrexed [26] and vinflunine [27], which have shown efficacy in cisplatin-pretreated patients. Vinflunine is currently being compared with the best supportive care as a second-line treatment after disease progression following platinum-based chemotherapy [27].

Although the GI regimen is not more active than the single-agent gemcitabine or ifosfamide given that less than six responses are obtained among these 23 patients, the level of antitumor activity observed in this study must be viewed with a consideration of the poor prognosis of patients with a universal cisplatin-refractory, rather than just cisplatin-pretreated, status and with frequent visceral metastases at the study entry. The GI regimen is associated with some severe toxicity, particularly myelosuppression, but these side effects are manageable. A positive aspect of GI for patients with metastatic UC is a reduced potential for renal toxicity. Renal impairment has been reported to be the most important factor preventing up to 40% of advanced UC patients from receiving active, cisplatin-containing treatment [28].

In conclusion, the GI regimen has an acceptable toxicity profile, but shows insufficient clinical activity in patients with cisplatin-refractory UC to warrant further testing. The search for other agents or combinations is definitely needed in the second-line setting in which no standard treatment exists.

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