Original article

A pilot study of gemcitabine and paclitaxel as third-line chemotherapy in metastatic urothelial carcinoma

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Abstract

Background: We evaluated the effectiveness of gemcitabine and paclitaxel therapy in patients with metastatic urothelial carcinoma for whom two lines of sequential chemotherapy had been unsuccessful.
Methods: A total number of 105 patients who had previously received first-line chemotherapy consisting of gemcitabine and cisplatin or carboplatin, were treated with second-line gemcitabine and docetaxel therapy between June 2006 and May 2015. Of these patients, 15 with an Eastern Cooperative Oncology Group Performance Status of 0 or 1 were administered gemcitabine and paclitaxel as third-line treatment from 2013 after failure of the second-line therapy. For each 21-day cycle, gemcitabine (1000 mg/m^2) was administered on days 1, 8, and 15, and paclitaxel (200 mg/m^2) on day 1. Patients were assessed for each cycle and any adverse events were noted. Furthermore, a Short Form Health Survey questionnaire was used to assess each patient's quality of life.
Results: Third-line gemcitabine and paclitaxel treatment cycles were undertaken for a median of four times (range 2–9). The disease control rate was 80.0%. After second-line gemcitabine and docetaxel therapy was completed, median progression-free survival and median overall survival were determined as 9.8 and 13.0 months, respectively. The only prognostic factor for overall survival, as determined by univariate and multivariate analyses, was third-line gemcitabine and paclitaxel therapy. Neutropenia (66.7%) and thrombocytopenia (53.3%) were noted as the grade 3 treatment-related toxicities. After two cycles of third-line gemcitabine and paclitaxel therapy, the pre- and post-treatment quality of life scores did not differ significantly.
Conclusions: Results demonstrate that third-line combination therapy using gemcitabine and paclitaxel is a feasible option for metastatic urothelial carcinoma patients.

Key words: gemcitabine and paclitaxel, metastasis, systemic chemotherapy, third-line, urothelial carcinoma

(J Rural Med 2017; 12(2): 105–111)

Introduction

Cisplatin-based systemic chemotherapy is the gold standard for the treatment of patients with metastatic urothelial carcinoma (mUC), which is a chemosensitive cancer. A combination regimen of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) has been used for the past two decades. A more recent, alternative standard treatment for mUC is the combination chemotherapy with gemcitabine and cisplatin (GC)[1–3]. However, long-term overall survival (OS) and progression-free survival (PFS) rates were deemed disappointing in long-term follow-up studies. Furthermore, a standard treatment for mUC does not exist, despite numerous reports describing the delivery of second-line chemotherapy after the failure of platinum-based, first-line chemotherapy in mUC patients[4–8]. Moreover, there is no standard second-line treatment for mUC outside the United States, where atezolizumab was FDA-approved in May 2016 for patients who had previously received platinum-based therapy[9].

The use of gemcitabine and docetaxel (GD) combination therapy as second-line treatment for mUC patients after failure of platinum-based chemotherapy as first-line treatment

has been previously reported by our group[10]. However, the efficacy of second-line GD therapy proved to be disappointing and thus, was never established as the standard treatment. Moreover, for patients with a good performance status (PS) after sequential GC and GD therapy, treatment options, unfortunately, are few. Consequently, the effectiveness of gemcitabine and paclitaxel (GP) combination therapy for mUC patients previously treated with two lines of sequential GC and GD chemotherapy was evaluated in this study.

Patients and Methods

Patients

We enrolled eligible patients with histologically-proven mUC of the urinary bladder or upper urinary tract who were admitted to hospital between June 2006 and May 2015. Patients had previously been surgically treated or had undergone biopsies of their primary lesions. Moreover, these patients had been treated with more than two cycles of chemotherapy with gemcitabine and cisplatin or carboplatin, which was completed a minimum of four weeks prior to enrollment. In total, 105 patients received second-line GD therapy, of which, 61 with an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1 who failed treatment after over two cycles of second-line GD therapy, were studied. Of the 61 enrolled patients, 15 underwent third-line GP therapy (third-line GP group), while the best supportive care only (BSC group) was provided to the remaining 46 patients. The following World Health Organization criteria were met by all the enrolled patients: an adequate bone marrow reserve (white blood cell [WBC] count > 3,500/μL, platelet count > 100,000/μL, and hemoglobin > 10 g/dL); reasonable hepatic function (serum bilirubin ≤ 1.5 mg/dL); and an estimated life expectancy of ≥ 12 weeks. Ineligible patients included those with non-malignant systemic disease, such as active infection that precluded them from receiving therapy, or those with any clinically significant cardiac arrhythmia, and/or congestive heart failure. All patients provided written informed consent prior to this clinical trial. The institutional chemotherapy review boards (ethical committees) of Nagoya City University Hospital and Nagoya City University (#984 and #1152, respectively) approved this study, which was conducted in accordance with the Declaration of Helsinki (according to the Tokyo revision, 2004).

Treatment schedule

Gemcitabine (1000 mg/m²) was administered to 15 patients by intravenous infusion for 30 min on days 1, 8, 15; paclitaxel (200 mg/m²) was also administered by intravenous infusion on day 1 according to Ikeda *et al*.[11]. Treat-

ments were repeated every 21 days. Dexamethasone (6.6 mg administered intravenously, 30 min before paclitaxel) and anti-allergic agents were used as pre-medications for paclitaxel. Full gemcitabine doses were administered on days 8 and 15 of each cycle, if patients displayed WBC and platelet counts > 3,000 and > 75,000 μL/mL, respectively; treatment was discontinued when lower count levels were present. The efficacy of a GP regimen as third-line chemotherapy was assessed in a follow-up analysis. Antiemetics and analgesics were included in the supportive care given to patients for adverse events.

Treatment evaluation

Creatinine clearance was measured prior each chemotherapy course, while blood counts and serum chemistries were measured weekly during treatment. Computed tomography (CT) was used to assess tumor sizes, as well as physical examinations. After each chemotherapy cycle, tumor sizes were remeasured. At least four weeks after administration of chemotherapy, each patient's response to treatment was evaluated. Tumor response, PFS, and OS were considered as the endpoints of this study.

Death, derived from medical records, was the endpoint for the measurement of OS and PFS rates. Time to failure was measured until the discontinuation of treatment, death, or progression. The Response Evaluation Criteria in Solid Tumors guidelines, version 1.1., were used to classify response[12]. A complete response (CR) occurred when all target lesions disappeared and any pathological lymph nodes had decreased in size (whether target or non-target) to < 10 mm along the short axis. A partial response (PR) was noted when the sum of diameters was decreased by at least 30% of target lesions. Progressive disease (PD) was defined as an increase in the sum of diameters by at least 20% of target lesions. In addition to the relative increase of 20%, the sum also had to show an absolute increase of at least 5 mm. The appearance of one or more new lesions was also considered as progression. The occurrence of insufficient shrinkage to qualify for PR and insufficient increase to qualify for PD indicated the existence of stable disease (SD). The National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0, were used to classify adverse events. In addition, a Short Form Health Survey questionnaire, before and two cycles of third-line GP treatment, was used to assess quality of life (QOL).

Statistics

Differences in categorical parameters were assessed using a Student *t*-test. Univariate statistical analyses were accomplished using chi-square test, and multivariate analyses were performed based on a stepwise regression. Cumulative

Table 1 Patients' characteristics and response rate

Characteristics		BSC group (n = 46)	Third-line GP group (n = 15)
Median age, years (range)		68 (37–82)	63 (51–80)
Gender, n (%)	Male	34 (73.9)	13 (86.7)
	Female	12 (26.1)	2 (13.3)
ECOG-PS at the end of 2nd-line GD therapy, n (%)	0	18 (39.1)	12 (80.0)
	1	28 (60.9)	3 (20.0)
Median eGFR at the end of 2nd-line GD therapy, (mL/min)/1.73 m^2 (range)		49.3 (14.1–101.5)	44.9 (9.0–75.7)
Visceral metastasis at the end of 2nd-line GD therapy, n (%)	Yes	18 (39.1)	7 (46.7)
	No	28 (60.9)	8 (53.3)
Response of second-line GD therapy, n (%)	PR	10 (21.7)	5 (33.3)
	SD	21 (45.7)	3 (20.0)
	PD	15 (32.6)	7 (46.7)
Response of third-line GP therapy, n (%)	PR		3 (20.0)
	SD		9 (60.0)
	PD		3 (20.0)

ECOG-PS: Eastern Cooperative Oncology Group Performance status, GD: Gemcitabine and docetaxel, eGFR: Estimated glomerular filtration rate, GP: Gemcitabine and paclitaxel, PR: Partial response, SD: Stable disease, PD: Progressive disease, BSC: Best supportive care.

rates were estimated using the Kaplan-Meier method, and the significance of differences between curves was tested by the log-rank test. A value of $p < 0.05$ was considered statistically significant. All the data were analyzed using SPSS® version 16.0 (SPSS Inc, Chicago, IL, USA).

Results

Treatment course and efficacy

Table 1 lists patients' clinical characteristics. A statistical significance was not found between the third-line GP and BSC groups, except for the proportion of good ECOG–PS patients in each group. The patient responses were assessed after they underwent two or more chemotherapeutic courses. Third-line GP chemotherapy was undertaken for a median of four treatment cycles (range 2–9). A PR was noted in three patients (20.0%) after third-line GP treatment and a median follow-up of 28 months. Table 1 shows that the objective response rate (ORR) was 20.0% and the disease control rate (% no. of PR and SD cases per total cases) was 80.0%. In the analysis focusing on the metastatic sites in 7 patients who had visceral metastases, four patients had lung metastasis alone and 3 patients had other metastases, such as bone and liver. Two out of 4 patients who only had lung metastasis showed SD, however, all patients who had other metastases showed PD.

Univariate and multivariate analyses for prognostic factors

Baseline parameters of the whole cohort were analyzed by univariate and multivariate analyses to elucidate predictive factors for OS. Table 2 shows the results of these analyses on the 61 second-line GD patients. The only prognostic factor for OS was found to be third-line GP therapy. For the third-line GP group, the median PFS was 9.8 months and the median OS was 13.0 months after second-line GD treatment had finished. Figures 1a and b show that the survival rate after 1 year of follow-up was 56.2%. In contrast, the median OS of the BSC group was 3.0 months (Figure 1c). Although, a direct comparison of the third-line GP therapy and BSC groups was not made because of the differences in the follow-up periods, it was noted that patients of the former group displayed an OS rate that surpassed that of the latter group (Figures 1b and c).

Adverse events and estimation of QOL

Table 3 lists hematological and other toxicities observed in the 15 third-line GP patients. The most common adverse event was myelosuppression, including predominant neutropenia. Ten patients (66.7%) were affected by grade 3 neutropenia that responded well to treatment with granulocyte-colony stimulating factor. Eight patients (53.3%) showed grade 3 thrombocytopenia and recovered in the absence of a platelet transfusion. Febrile neutropenia was not evident. Eleven patients (73.3%) experienced a < grade 3 neuropathy. Deaths related to treatment were not noted.

Table 4 outlines QOL scores using a Medical Outcomes

Table 2 Univariate and multivariate analyses of baseline parameters and overall survival in 61 second-line GD treated patients

Parameter	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
Age, < 69 vs. 70 ≤	1.15	0.63–2.01	0.65	1.22	0.62–2.42	0.56
Gender, male vs. female	0.85	0.43–1.67	0.64	0.86	0.40–1.83	0.70
eGFR at the end of second-line GD, < 60 vs. 60 ≤	2.11	1.16–3.82	< 0.05*	1.94	0.92–4.11	0.08
No. of first-line cycles, < 4 vs. 5 ≤	0.82	0.46–1.50	0.52	1.34	0.68–2.66	0.40
No. of second-line cycles, < 4 vs. 5 ≤	0.54	0.30–0.98	< 0.05*	0.66	0.33–1.32	0.24
ECOG-PS at the end of second-line GD, 0 vs. 1	1.66	0.93–2.95	0.09	1.06	0.54–2.06	0.87
third-line GP therapy, yes vs. no	0.21	0.09–0.50	< 0.001**	0.20	0.08–0.52	< 0.001**

eGFR: Estimated glomerular filtration rate, GD: Gemcitabine and docetaxel, ECOG-PS: Eastern Cooperative Oncology Group Performance Status, GP: Gemcitabine and paclitaxel, HR: Hazards ratio, CI: Confidence interval. *$p < 0.05$, **$p < 0.001$ indicates a significant difference.
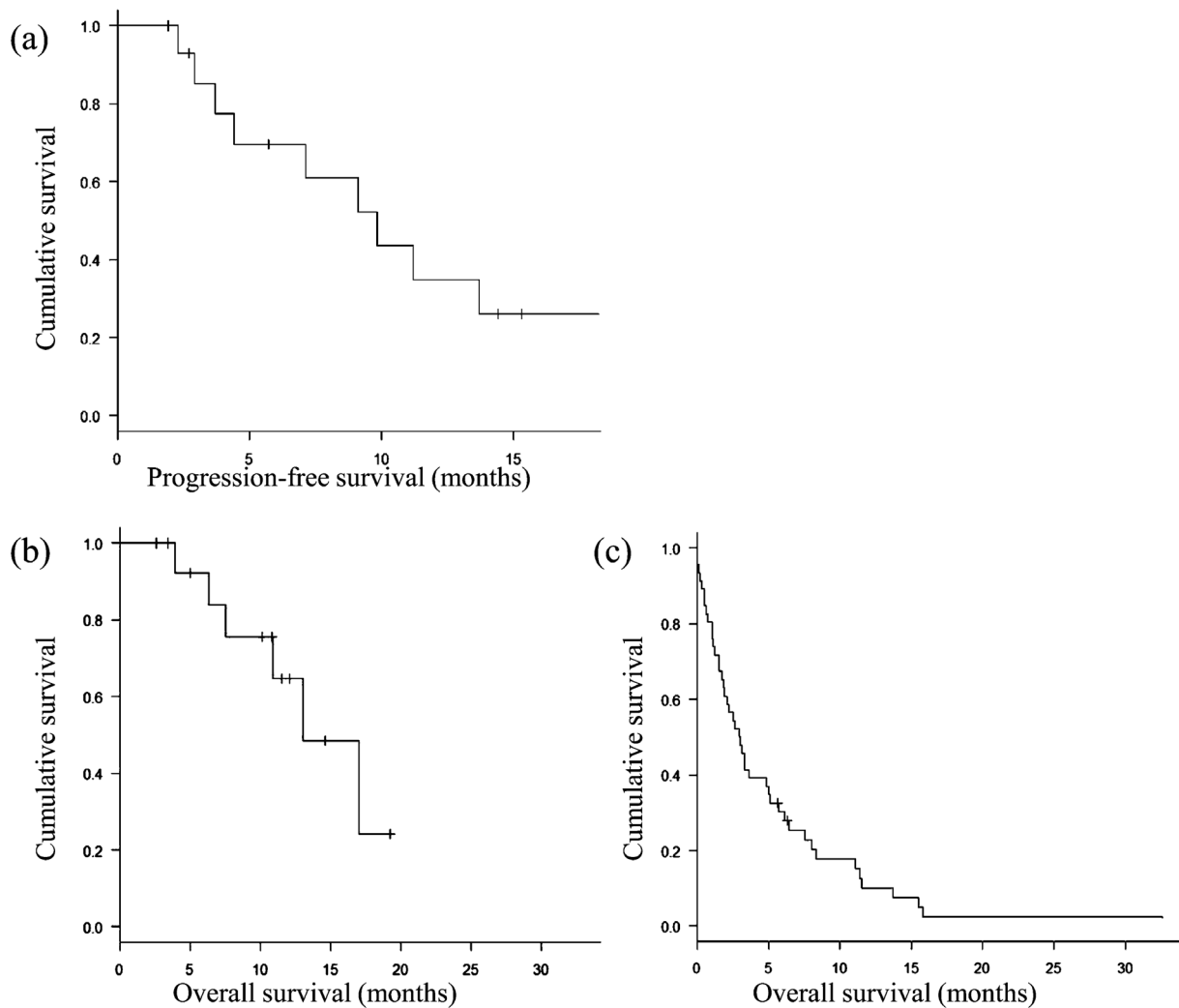

Figure 1 Kaplan-Meier curves of progression-free survival (PFS) and overall survival (OS) in metastatic urothelial cancer patients after the failure of second-line GD therapy. (a) PFS when GP was used as third-line chemotherapy. (b) OS when GP was used as the third-line chemotherapy. (c) OS for the BSC group. GD: Gemcitabine and docetaxel, GP: Gemcitabine and paclitaxel, BSC: Best supportive care.

Study (MOS) 36-item Short Form Health Survey questionnaire. After comparing two cycles of third-line GP therapy to pre-treatment, mean norm-based scores (NBSs) of eight items were found not to be significantly decreased. We therefore conclude that patients' QOL was not significantly degraded after two cycles of third-line GP treatment.

Table 3 Adverse events in all 15 patients who were treated with gemcitabine and paclitaxel as third-line chemotherapy for metastatic urothelial carcinoma

Toxicity	Grade (all cycles), no. of patients (%)			
	1	2	3	4
Hematologic				
Neutropenia		5 (33.3)	10 (66.7)	
Anemia		1 (6.7)		
Thrombocytopenia		3 (20.0)	8 (53.3)	
Non-hematologic				
Nausea/vomiting	4 (26.7)			
Gastritis	8 (53.3)			
Neuropathy	10 (66.7)	1 (6.7)		
Alopecia		4 (26.7)		

Discussion

Although metastatic urothelial carcinoma (mUC) is sensitive to the use of cisplatin as first-line chemotherapy, this sensitivity does not last. Recently, GP therapy has been used as second-line treatment for mUC in several institutions[4]. However, only a few reports have described a salvage chemotherapy regimen after the failure of two lines of systemic chemotherapy. Table 5 summarizes the findings of five reports that evaluated the efficacy and toxicity of third-line chemotherapy for mUC[13–17]. However, only Joung et al.[14] described a case of CR. We, therefore, evaluated tumor control according to the proportion of PR and SD cases to the total number of cases. Differences between patients' backgrounds and treatment strategies between our and others' studies made a direct comparison difficult. Regardless, the tumor response, PFS, and OS rates achieved in response to third-line GP therapy in these studies surpassed the results of other treatments used. Third-line GP therapy appeared safe with regard to the toxicities that developed; however, grade 4 hematological or other types of adverse events did not occur, and chemotherapy did not induce life-threaten-

Table 4 Evaluation of QOL scores using a MOS 36-item Short Form Health Survey questionnaire

Items	Pre third-line GP therapy (Mean NBS score ± SD)	After two cycles of third-line GP therapy (Mean NBS score ± SD)	p value
Physical function	36.4 ± 13.7	36.2 ± 15.3	0.99
Physical role	35.3 ± 15.3	34.2 ± 12.4	0.83
Bodily pain	38.5 ± 6.5	38.8 ± 9.0	0.90
General health	34.9 ± 6.0	34.8 ± 9.2	0.96
Vitality	32.3 ± 9.3	33.3 ± 15.3	0.82
Social functioning	29.5 ± 19.1	30.8 ± 14.9	0.84
Emotional role	32.2 ± 17.0	31.9 ± 12.0	0.99
Mental health	31.4 ± 11.2	33.0 ± 13.1	0.72

GP: Gemcitabine and paclitaxel, NBS: Norm-based scoring, QOL: quality of life, MOS: Medical Outcomes Study, SD: standard deviation.

Table 5 Summary of sequential chemotherapy trials against advanced or metastatic urothelial carcinoma

Author	second-line regimen	third-line regimen	No. of patients	No. of PR patients (%)	No. of RR patients (%)	Median PFS (months)	Median OS (months)
Soga et al.[12]	carboplatin / paclitaxel	gemcitabine	13	1 (7.7)	8 (61.5)	2.0	7.3
Joung et al.[13]	MVAC, or GC	paclitaxel / cisplatin	21	3 (14.3)	9 (42.9)	3.0	9.0
Rozzi et al.[14]	carboplatin / paclitaxel, or paclitaxel	PLD	23	3 (13.0)	10 (43.5)	4.1	6.3
Matsumoto et al.[15]	gemcitabine / paclitaxel	gemcitabine / nedaplatin	10	1 (10.0)	4 (40.0)	5.0	8.8
Iida et al.[16]	gemcitabine / docetaxel	pemetrexed	4	0 (0)	0 (0)	1.9	–
Current trial	gemcitabine / docetaxel	gemcitabine / paclitaxel	15	3 (20.0)	12 (80.0)	9.8	13.0

SD: stable disease, PR: partial response, RR: relative response (PR and SD cases), PFS: progression free survival after the end of second-line chemotherapy, OS: overall survival after the end of second-line chemotherapy, MVAC: methotrexate, vinblastine, doxorubicin, and cisplatin, GC: gemcitabine and cisplatin, PLD: pegylated liposomal doxorubicin.

ing complications. Consequently, we recommend third-line therapy for mUC patients who have undergone two consecutive GC and GD chemotherapies, and demonstrated good performance status.

Gemcitabine was consistently used in three consecutive regimens as it was the main focus of our strategy of sequential chemotherapy. As the predominant feature of our sequential chemotherapy strategy, gemcitabine was consistently used in three consecutive regimens. Recently, mechanisms of acquisition of chemoresistance to gemcitabine in urothelial cancer cells have been outlined[18, 19]. However, gemcitabine shows a synergistic effect when combined with different chemotherapeutic agents; therefore, we consistently used gemcitabine in our chemotherapeutic strategies for mUC. As a result, GD therapy after the failure of GC therapy showed good anti-tumor effects as described by a previous study[10]. In this study, GP therapy after the failure of second-line GD therapy displayed an efficacy in terms of an anti-tumor effect and prolonged patient survival. The efficacy of paclitaxel against docetaxel-resistance has also been reported in breast cancer[20]. We observed median OS rates of 65.8 and 56.4 months from the start of first-line chemotherapy and second-line chemotherapy, respectively. Sequential therapy using gemcitabine and switching taxane derivatives may be highly efficacious in mUC. However, future studies with larger patient cohorts and more detailed *in vitro* investigations of drug mechanisms are required.

Elderly patients over 70 years of age often develop metastases associated with UC. Therefore, estimating QOL is critical in the face of developing long-term systemic chemotherapy, despite the lack of an established standard protocol for estimating QOL in this patient cohort. In this study, a MOS 36-item Short Form Health Survey questionnaire was used. Significantly decreased NBSs for all items were not evident after two cycles of third-line GP therapy as shown in Table 4. As an adverse event, neuropathy was characteristic of GP therapy, but this was well-tolerated with supportive care. Total supporting care to uphold patients' QOL is required in conjunction with chemotherapy when a long-term course of therapy is undertaken.

Several limitations were evident in our study. For example, the patient cohort used was very small with the selected cases, and the study itself was undertaken in a retrospective manner. Despite this, our findings suggest that sequential chemotherapy using GD and GP after the failure of first-line chemotherapy with cisplatin for mUC is safe and effective. Bearing in mind the safety and benefit profiles, including QOL, observed in this study of GP therapy, further prospective trials are warranted to evaluate this strategic sequential chemotherapy approach for mUC patients. In conclusion, for mUC patients previously treated with GC and GD se-

quential therapy, combination therapy with gemcitabine and paclitaxel appears to be well-tolerated and shows activity against disease.

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