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Original Article

The Combination of Gemcitabine, Cisplatin, and Paclitaxel as Salvage Chemotherapy for Advanced Urothelial Carcinoma

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There is no standard second-line or salvage treatment for advanced urothelial carcinoma (UC). Here we investigated the efficacy and safety of gemcitabine, cisplatin, and paclitaxel (GCP) combination chemotherapy as salvage chemotherapy for advanced UC. We retrospectively analyzed the cases of 23 patients with advanced UC who showed progression or recurrence after cisplatin-based chemotherapy. Gemcitabine (1000 mg/m^2), and paclitaxel (80 mg/m^2) were administered on days 1 and 8. Cisplatin (70 mg/m^2) was administered on day 1. The 3-week cycle regimen was repeated until disease progression if it had no intolerable toxicity. The overall response rate was 61% (95%CI, 41-78%). The median overall survival and progression-free survival times were 14 months and 5.5 months, respectively. Of the already known risk factors of chemotherapy for advanced UC, only the performance status was a prognostic factor for OS. Overall, 16 of the 23 patients (70%) experienced grade 3/4 toxicities, and no fatal adverse events were observed. GCP therapy was a promising option as second-line or salvage therapy for advanced UC.

Key words: urothelial carcinoma, gemcitabine, cisplatin, paclitaxel, second-line, salvage

Metastatic or advanced urothelial carcinoma (UC) has become a more common disease in Japan as the percentage of elderly citizens continues to increase. This carcinoma is life-threatening, with a median survival time of <6 months without treatment. In the efforts to identify an effective treatment for advanced UC, the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) showed modest improvement as a first-line chemotherapy [1]. In 2000, the combination of gemcitabine and cisplatin (GC) was reported as a newly promising therapy providing similar survival times and better tolerability compared to MVAC [2]. GC and MVAC are the gold standard treatments for metastatic or advanced UC as first-line chemotherapy with the initial high response rate of 50% and the median progression-free survival (PFS) and overall survival (OS) of 8 months and 14 months, respectively [2,3]; however, most of the patients who received these first-line chemotherapies relapsed and required additional therapy. There are as yet no standard second-line treatments or salvage therapy for metastatic or advanced UC.

Single-agent taxane or gemcitabine or a combination of them are commonly used as second-line or salvage therapy for metastatic or advanced UC. Single-arm phase II trials reported that single-agent taxane therapies resulted in a moderate response rate of 10-20% and an OS rate of 6-9 months [4,5]. Taxane showed a more improved OS when used in combina-

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tion with other agents compared to its single use [6]. Although taxane could be a key drug in the future as a second-line chemotherapy for metastatic or advanced UC, cisplatin is thought to have some beneficial effect on some patients even after the failure of cisplatin-based chemotherapy. As there is no useful biomarker to predict cisplatin sensitivity or resistance, cisplatin should be included after first-line chemotherapy considering its marked effect on urothelial carcinoma.

In light of this background, we designed the combination of gemcitabine, cisplatin, and paclitaxel (GCP) for patients with advanced UC after the failure of a platinum-based regimen. This is the first study to investigate the efficacy and safety of GCP treatment as a salvage therapy for advanced UC.

Some studies have attempted to identify the prognostic factors in chemotherapy for advanced UC. The most likely potential factors are the Eastern Cooperative Oncology Group performance status (ECOG PS), hemoglobin (≤10 g/dL vs. >10 g/dL), albumin (≤the lower limit of normal vs. >the lower limit of normal), the presence of liver metastases, and the time from prior chemotherapy (TFPC) (≤3 months vs. >3 months) [7, 8]. We also investigated whether these five factors could be prognostic factors in advanced UC patients treated with GCP.

Patients and Methods

Study population. A total of 23 patients who received the GCP regimen as second-line or third-line chemotherapy for advanced or metastatic UC were included in this study. All of the patients showed progressive disease after prior platinum-based therapy (MVAC or GC) in a perioperative or metastatic setting. In a perioperative setting, first-line chemotherapy was administered in 2 or 3 cycles as neoadjuvant or adjuvant chemotherapy. Second-line chemotherapy or GCP treatment was administered when metastasis or local recurrence appeared in the course of follow-up. GCP treatment as third-line chemotherapy was administered when progressive disease was shown on radiological images in the course of or after second-line chemotherapy.

In the cases with metastasis, first-line chemotherapy was administered as long as it was observed to be effective on radiological images. Second-line chemotherapy or GCP treatment was administered when progressive disease was shown on radiological images in the course of or after first-line chemotherapy. GCP treatment as third-line chemotherapy was administered when progressive disease was seen on radiological images in the course of or after second-line chemotherapy.

Each patient's UC had to have been proved histologically prior to the administration of the GCP treatment. The GCP treatment was administered between January 2011 and December 2016 at Hiroshima City's Hiroshima Citizens Hospital, and we reviewed the patients' medical records retrospectively. The study protocol was approved by the Ethics Committee of Hiroshima Citizens Hospital (approval no. 29-29).

Treatment schedule. Gemcitabine and paclitaxel were administered at 1000 mg/m^2 and 80 mg/m^2, respectively on days 1 and 8. Cisplatin was administered at 70 mg/m^2 on day 1. This regimen was continued as long as it was effective objectively and the toxicity was tolerable. These regimen doses were decreased according to the patients' renal function and the extent of adverse events.

Patient evaluation. We obtained the patients' demographic data and treatment details from the medical records. Age, gender, ECOG PS, the primary site of the tumor, metastatic site(s) of the tumor, prior therapies, and baseline laboratory data were included in the demographic data. Treatment response, number of cycles, the date of progression, and the date of death were included in the GCP treatment details. All treatment-associated toxicity data specifically on hematologic toxicity rates and febrile neutropenia were recorded. Tumor responses were assessed using Response Evaluation Criteria in Solid Tumors (RECIST, ver. 1.1), classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The best overall response on RECIST was recorded as the treatment response. Toxicity was assessed using the U.S. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, ver. 3.0).

Statistical analysis. We defined the responders as CR + PR. We defined OS as the time from the start of GCP treatment to the date of death, and PFS was defined as the time from the start of GCP treatment to the date of objective progression. The cases of the patients who were still alive at the date of the last follow-up were censored. OS and PFS were estimated by the Kaplan-Meier method. We assessed the variables

with potential as prognostic factors (*i.e.*, the ECOG PS, hemoglobin, albumin, the TFPC, and the presence of liver metastasis) for OS and PFS by performing univariate and multivariate analyses with a Cox regression model. All statistical analyses were performed with the JMP 10 program (SAS, Cary, NC). Statistical significance was defined by a p-value < 0.05.

Results

Patient characteristics. The baseline characteristics of the patients are summarized in Table 1. Thirteen of the 23 patients (57%) had an ECOG PS of ≥1. Five patients had liver metastasis, and visceral metastasis were seen in 16 patients. The GCP regimen was administered in 21 patients (91%) as second-line chemotherapy after a GC regimen, and the other two patients (9%) received the GCP regimen as third-line chemotherapy after GC and MVAC regimens. The median follow-up period was 12 months (range 3-55 months).

Table 1 Baseline patient characteristics

Characteristics	Number of patients (%)
Age	
<70 years	10 (43%)
≥70 years	13 (57%)
Gender	
Male	19 (83%)
Female	4 (17%)
ECOG-PS	
0	10 (43%)
1	10 (43%)
≥2	3 (14%)
Site of primary tumor	
Bladder	9 (39%)
Ureter	5 (22%)
Renal pelvis	9 (39%)
Site of recurrence or metastasis	
Local	4
Lymphnode	16
Lung	11
Liver	5
Bone	5
Muscle	2
Prior choemotherapy	
GC	21 (91%)
GC+MVAC	2 (9%)
Purpose of prior chemotherapy	
Neoadjuvant	8
Adjuvant	12
For recurrence or metastasis	7
TFPC	
<3 months	8 (35%)
≥3 months	15 (65%)

Efficacy. The overall response rate to GCP therapy was 61% (Table 2). All 14 patients of these responders showed a PR. The PR rates in individual metastatic sites are presented in Table 3. The PR rates of the liver metastasis and lung metastasis were 80% and 55%, respectively.

The median OS and PFS rates were 14.0 months (95% confidence interval [CI]: 9-23 months) and 5.5 months (95%CI 4-7 months), respectively (Fig. 1).

Treatment administration and toxicity. The average number of GCP treatments administered was 3.5 (range 1-8). The frequencies of grade 3 or higher adverse events are shown in Table 4. Grade 3/4 toxicities were observed in 70% (n=16) of the 23 patients, and no fatal adverse events were observed. Grade 3-4 anemia, neutropenia, and thrombocytopenia occurred in 21%, 47%, and 39% of patients, respectively. No patients had febrile neutropenia. The major reasons for the discontinuation of GCP treatment were progressive disease (48%) and the patient's request for outpatient treatment (22%). The other reasons for discontinuation could not be discerned from the medical records.

Association of factors with overall and progression-free survival. The univariate analyses identified only the ECOG PS as significantly associated with OS (Table 5). In the multivariate analyses, the ECOG PS was an independent prognostic factor for OS with the hazard ratio of 6.5 (95%CI 1.5-33.7, $p=0.012$). All of the other 4 prognostic factors were not significantly associated with OS or PFS.

Table 2 Response for GCP

RECIST evaluation	Number of patients (%)
CR	0 (0%)
PR	14 (61%)
SD	6 (26%)
PD	3 (13%)

Table 3 Rates of partial response in each site of metastasis

Site of metastasis	Number	Number of PR (%)
Liver	5	4 (80)
Lung	11	6 (55)
Lymphnode	16	6 (38)
Local	4	3 (75)
Muscle	2	1 (50)

Discussion

In the era of GC treatment as first-line chemotherapy for advanced UC, there is no standard treatment as a second-line chemotherapy. Changing agents from prior regimens or adding new agents is a basic strategy to maintain efficacy in the subsequent therapy. For instance, the use of the MVAC regimen after progression or relapse following GC treatment produced a response rate of 30%, with the median PFS and OS rates of 5.3 and 10.9 months, respectively [9]. In our study, GC was used as the first-line chemotherapy in 21 (91%) patients, and 61% of the patients showed a PR with the median PFS and OS rates of 5.5 and 14 months, respectively. Although only paclitaxel was added to the first-line GC treatment, the GCP regimen produced a better response with more tolerable toxicity than MVAC.

Paclitaxel has been the most commonly used drug in second-line or salvage therapy in advanced UC. The combination of paclitaxel and other drugs has been confirmed to exert more efficacy in the salvage setting [6]. In the several combinations of paclitaxel and other drugs, the combination of gemcitabine and paclitaxel (GP) is the most acceptable therapy [10]. Several

Table 4 Laboratory toxicity rates

	Grade 3	Grade 4
	Number of patients (%)	Number of patients (%)
Anemia	5 (21%)	0 (0%)
Leukopenia	9 (39%)	2 (30%)
Neutropenia	4 (17%)	7 (30%)
Febrile neutropenia	0 (0%)	0 (0%)
Thrombocytopenia	3 (13%)	6 (26%)
Hyponatremia	1 (4%)	1 (4%)
Hypokalemia	1 (4%)	0 (0%)

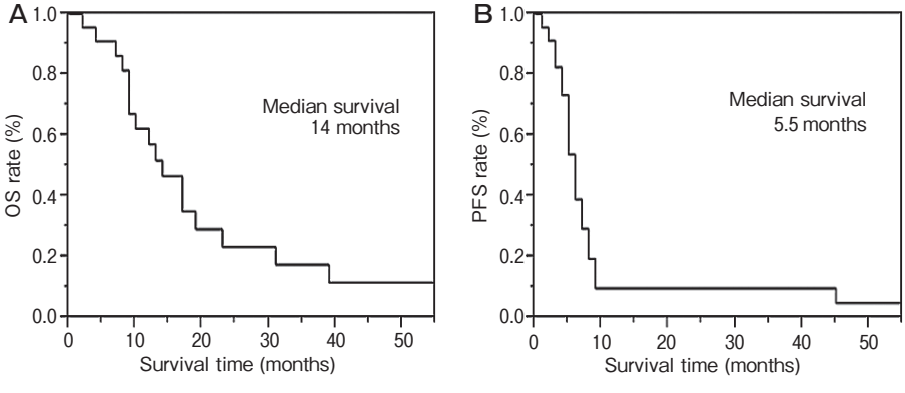

Fig. 1 **A**, Overall survival in GCP treatment; **B**, Progression free survival in GCP treatment.

Table 5 Univariable analyses for association of valiables with overall and progression -free survival

Factor	Type	HR (95% CI)	*p* value
Overall survival			
ECOG PS	>0 vs 0	4.4 (1.4–16.7)	0.009*
Hemoglobin	<10 vs ≥10	1.2 (0.2–4.3)	0.9
Albumin	Below LLN vs normal	2.2 (0.8–6.5)	0.1
Time from prior chemotherapy	<3 vs ≥3 months	1.7 (0.6–4.3)	0.3
Liver metastasis	Yes vs no	0.9 (0.2–2.8)	0.9
Progression-free survival			
ECOG PS	>0 vs 0	2.1 (0.8–5.7)	0.1
Hemoglobin	<10 vs ≥10	1.1 (0.2–3.8)	0.9
Albumin	Below LLN vs normal	1.6 (0.6–4.5)	0.1
Time from prior chemotherapy	<3 vs ≥3 months	1.3 (0.5–3.1)	0.3
Liver metastasis	Yes vs no	0.7 (0.2–2.2)	0.6

Asterisk indicates statistical significance ($p < 0.05$); LLN = lower limit of normal (LLN of Albumin: 4.0 g/dl)
Unit of Hemoglobin: g/dl Unit of Albmin: g/dl

phase II trial showed that GP combination therapy can provide an objective response rate ranging from 33% to 60%, a median OS rate of 9-14.4 months, and a median PFS of 4-11 months [11-15]. The GCP triplet therapy examined in our present study showed almost the same efficacy as that of GP combination therapy. In basic research using bladder cancer cell lines, however, the effects of cisplatin could be optimized by combination with paclitaxel [16]. Some patients are still cisplatin-sensitive even after recurrence or relapse following a cisplatin-based regimen.

In our prognostic factor analyses, the TFPC was not revealed as a significant independent prognostic factor for PFS and OS following GCP treatment, which suggests that patients can still be sensitive to cisplatin even after early recurrence or relapse following a cisplatin-based regimen.

As for toxicity, phase II trials of combination therapy of gemcitabine and paclitaxel showed the following percentages: grade 3-4 anemia, 0-28%; neutropenia, 16-46%; and thrombocytopenia, 0-16%. Febrile neutropenia ranged from 7% to 16% [11-15]. In our present analysis of GCP treatment, neutropenia and thrombocytopenia were observed at relatively high frequencies, but they were dealt with in the clinical setting without the development of any severe clinical problems.

The limitations of this study were the small number of patients (n=23) and the retrospective design. Nevertheless, the results of our analyses of the patients' GCP treatment suggested that this therapy has good efficacy as a salvage treatment for advanced UC. Prospective and large cohort studies are needed to reveal biomarkers that will identify the maximum benefit of GCP treatment.

References

1. Loehrer PJ, Sr., Einhorn LH, Elson PJ, Crawford ED, Kuebler P, Tannock I, Raghavan D, Stuart-Harris R, Sarosdy MF and Lowe BA, *et al.*: A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol (1992) 10: 1066–1073.
2. Maase Hvd, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, Bodrogi I, Albers P, Knuth A, Lippert CM, Kerbrat P, Rovira PS, Wersall P, Cleall SP, Roychowdhury DF, Tomlin I, Visseren-Grul CM and Conte PF: Gemcitabine and Cisplatin Versus Methotrexate, Vinblastine, Doxorubicin, and Cisplatin in Advanced or Metastatic Bladder Cancer: Results of a Large, Randomized, Multinational, Multicenter, Phase III Study. J Clin Oncol (2000) 18: 3068–3077.
3. Maase Hvd, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, Moore MJ, Zimmermann A and Arning M: Long-Term Survival Results of a Randomized Trial Comparing Gemcitabine Plus Cisplatin, With Methotrexate, Vinblastine, Doxorubicin, Plus Cisplatin in Patients With Bladder Cancer. J Clin Oncol (2005) 23: 4602–4608.
4. Vaughn DJ, Broome CM, Hussain M, Gutheil JC and Markowitz AB: Phase II trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer. J Clin Oncol (2002) 20: 937–940.
5. McCaffrey JA, Hilton S, Mazumdar M, Sadan S, Kelly WK, Scher HI and Bajorin DF: Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. J Clin Oncol (1997) 15: 1853–1857.
6. Sonpavde G, Pond GR, Choueiri TK, Mullane S, Niegisch G, Albers P, Necchi A, Di Lorenzo G, Buonerba C, Rozzi A, Matsumoto K, Lee JL, Kitamura H, Kume H and Bellmunt J: Single-agent Taxane Versus Taxane-containing Combination Chemotherapy as Salvage Therapy for Advanced Urothelial Carcinoma. Eur Urol (2016) 69: 634–641.
7. Bellmunt J, Choueiri TK, Fougeray R, Schutz FAB, Salhi Y, Winquist E, Culine S, Maase Hvd, Vaughn DJ and Rosenberg JE: Prognostic Factors in Patients With Advanced Transitional Cell Carcinoma of the Urothelial Tract Experiencing Treatment Failure With Platinum-Containing Regimens. J Clin Oncol (2010) 28: 1850–1855.
8. Sonpavde G, Pond GR, Fougeray R, Choueiri TK, Qu AQ, Vaughn DJ, Niegisch G, Albers P, James ND, Wong YN, Ko YJ, Sridhar SS, Galsky MD, Petrylak DP, Vaishampayan UN, Khan A, Vogelzang NJ, Beer TM, Stadler WM, O'Donnell PH, Sternberg CN, Rosenberg JE and Bellmunt J: Time from Prior Chemotherapy Enhances Prognostic Risk Grouping in the Second-line Setting of Advanced Urothelial Carcinoma: A Retrospective Analysis of Pooled, Prospective Phase 2 Trials. Eur Urol (2013) 63: 717–723.
9. Sonpavde G, Pond GR, Rosenberg JE, Bajorin DF, Regazzi AM, Mullane SA, Niegisch G, Albers P, Necchi A, Lorenzo Gd, Fougeray R, Ko Y-J, Rozzi A, Matsumoto K, Lee J-L, Kitamura H, Kume H, Milowsky MI, Choueiri TK and Bellmunt J: Externally validated improved 5-factor prognostic model in patients (pts) receiving salvage systemic therapy for advanced urothelial carcinoma (UC). J Clin Oncol (2015) 33: 4527–4527.
10. Han KS, Joung JY, Kim TS, Jeong IG, Seo HK, Chung J and Lee KH: Methotrexate, vinblastine, doxorubicin and cisplatin combination regimen as salvage chemotherapy for patients with advanced or metastatic transitional cell carcinoma after failure of gemcitabine and cisplatin chemotherapy. Br J Cancer (2008) 9: 86–90.
11. Narayanan S, Harshman LC and Srinivas S: Second-line therapies in metastatic urothelial carcinoma. Hematol Oncol Clin North Am (2015) 29: 341–359.
12. Fechner G, Siener R, Reimann M, Kobalz L and Albers P: Randomised phase II trial of gemcitabine and paclitaxel second-line chemotherapy in patients with transitional cell carcinoma (AUO Trial AB 20/99). Int J Clin Pract (2006) 60: 27–31.
13. Kanai K, Kikuchi E, Ohigashi T, Miyajima A, Nakagawa K, Nakashima J and Oya M: Gemcitabine and paclitaxel chemotherapy for advanced urothelial carcinoma in patients who have received prior cisplatin-based chemotherapy. Int J Clin Oncol (2008) 13: 510–514.
14. Meluch AA, Greco FA, Burris HA, 3rd, O'Rourke T, Ortega G, Steis RG, Morrissey LH, Johnson V and Hainsworth JD: Paclitaxel and gemcitabine chemotherapy for advanced transitional-cell carcinoma of the urothelial tract: a phase II trial of the Minnie pearl cancer research network. J Clin Oncol (2001) 19: 3018–3024.
15. Sternberg CN, Calabro F, Pizzocaro G, Marini L, Schnetzer S and Sella A: Chemotherapy with an every-2-week regimen of gemcitabine and paclitaxel in patients with transitional cell carcinoma who have received prior cisplatin-based therapy. Cancer (2001) 92: 2993–2998.
16. Takahashi T, Higashi S, Nishiyama H, Segawa T, Nakamura E, Kinoshita H, Itoh N, Yamamoto S, Kamoto T, Habuchi T and Ogawa O: Biweekly paclitaxel and gemcitabine for patients with advanced urothelial cancer ineligible for cisplatin-based regimen. Jpn J Clin Oncol (2006) 36: 104–108.
17. Pu YS, Chen J, Huang CY, Guan JY, Lu SH and Hour TC: Cross-resistance and combined cytotoxic effects of paclitaxel and cisplatin in bladder cancer cells. J Urol (2001) 165: 2082–2085.