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ORIGINAL ARTICLE

Comparison of efficacy and toxicity of second-line combination chemotherapy regimens in patients with advanced urothelial carcinoma

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Abstract

Background The aim of this study was to evaluate the efficacy and toxicities of second-line chemotherapy regimens with docetaxel and gemcitabine (GD), or paclitaxel and gemcitabine (GP) for advanced or metastatic urothelial carcinoma (UC) that did not respond to first-line platinum-based chemotherapy.

Methods From 2002 to 2017, 78 patients with metastatic UCs that progressed after platinum-based chemotherapy were treated with either GD ($n=41$) or GP ($n=37$). We compared these two different regimens by analyzing their efficacy and toxicities in a retrospective manner.

Results Of the 78 patients enrolled in this study, it was possible to determine treatment efficacy in 70; the proportion of patients with objective response and disease control were 8.6 (9/70) and 54.3% (38/70), respectively. The median progression-free survival and overall survival in the total population (GP and GD) were 3.5 (95% CI 0.6–53.3) and 9.6 months (95% CI 1.2–53.3), respectively. There was no significant difference between the two regimens (GD or GP) regarding survival outcomes. Treatment-related adverse events were mostly manageable, but one patient died as a result of febrile neutropenia. The presence of liver metastasis and anemia (Hb < 10.0 g/dl) was prognostic factors for worse survival.

Conclusions Combination chemotherapy with either GP or GD was a favorable and well-tolerated second-line treatment regimen for patients with advanced or metastatic UC following the failure of a platinum-based regimen. Further study using a large prospective cohort is needed to identify patients who will benefit from second-line combination therapy.

Keywords Bladder cancer · Chemotherapy · Docetaxel · Paclitaxel

Introduction

Cisplatin-based chemotherapy is regarded as the gold standard for treatment of patients with advanced or metastatic urothelial carcinoma (UC) [1]. The regimen of methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) has been widely used as first-line chemotherapy [2]. More recently, combination therapy with gemcitabine and cisplatin (GC) has become standard first-line chemotherapy [3, 4]. However, there is no standard second-line treatment for patients who experience cancer progression after platinum-based chemotherapy until the recent approval of pembrolizumab as a second-line treatment drug for metastatic urothelial carcinoma [5, 6]. Although many regimens that include docetaxel, paclitaxel, gemcitabine, and vinflunine have been used in a second-line setting, as yet no randomized phase III trials with adequate comparator arms have been conducted to assess the true value and overall survival (OS) benefits of second-line combination therapy [7–10].

Previous studies showed that treatment with a single agent, such as docetaxel or paclitaxel, yielded modest effects, but combination therapy of paclitaxel or docetaxel with gemcitabine (GP or GD) showed better results [8, 11–13]. Progression-free survival (PFS) and OS in a

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randomized phase III trial for GP-treated patients were reported as 3.1 and 8.0 months, respectively [8]. In another study, Naiki et al. [14] reported that PFS and OS in GD-treated patients were 4.4 and 10.8 months, respectively. In a KEYNOTE trial, treatment with pembrolizumab prolonged the OS of bladder cancer patients by about 3 months over single-agent chemotherapy using paclitaxel, docetaxel, or vinflunine [6]. This is probably because single-agent chemotherapy is recommended in National Comprehensive Cancer Network and European Association of Urology guidelines in a second-line setting.

So far, there have been no trials to compare the efficacy between GP and GD as second-line treatments. In our hospital, we have used either GD or GP to treat patients who experience tumor progression after platinum-based combination chemotherapy since 2002. In the present study, we retrospectively evaluated the efficacy and toxicity of GD and GP regimens as a second-line chemotherapy for advanced or metastatic UC patients. Furthermore, we analyzed the factors which affected the survival time and treatment-related adverse events of the patients who received GD or GP combination therapy in a retrospective manner.

Patients and methods

Patients eligible for the present study had histologically confirmed metastatic UC of the urinary bladder or upper urinary tract. Patients who experienced tumor recurrence or progression after cisplatin-based chemotherapy, with or without radical surgery (cystectomy or nephroureterectomy), were included. Patients who developed recurrence or progressed within 12 months after the receipt of platinum-based neoadjuvant or adjuvant chemotherapy were also included. Patients who had received prior second-line chemotherapy were excluded from the present study. Between September 2002 and December 2017, 189 patients with advanced or metastatic UC had received the first line, platinum-based chemotherapy. Seventy-eight out of 189 (41.2%) patients were eligible for treatment with the second line GD/GP therapies. Further inclusion criteria were ECOG performance status ≤ 2, life expectancy ≥ 12 weeks, white blood cell count $\geq 3{,}000/\mu l$, and adequate hepatic function. Paclitaxel and docetaxel were used in Osaka City University hospital under the approval of institutional review board (no. 139 and 371, respectively) until the approval by Ministry of Health, Labor and Welfare in 2014 in Japan. Written informed consent was obtained from all patients before they received this therapy. This study was approved by the institutional review board at Osaka City University Hospital in accordance of with the Declaration of Helsinki (No. 3959).

Treatment schedule and evaluation

GD-treated patients received 70 mg/m^2 of docetaxel on day 1 and 1000 mg/m^2 of gemcitabine on days 1 and 8 of each 21-day cycle. GP-treated patients received 200 mg/m^2 of paclitaxel on day 1 and 1000 mg/m^2 of gemcitabine on days 1, 8, and 15 of each 28-day cycle. Between September 2002 and January 2010, GP was selected as a standard regimen for second-line treatment in our hospital, but GD became the standard after 2010, because we observed relatively high incidences of neuro-toxic adverse events in GP-treated patients. Radiographic examinations (computed tomography, magnetic resonance imaging, or bone scan) were performed every 2–3 cycles of treatment, and tumor response and disease progression were measured according to the Response Evaluation Criteria in Solid Tumors (RECIST) ver 1.0, since many cases were evaluated before 2009. Using medical records, OS and PFS were measured until death or progression, respectively. Complete response (CR) was defined as disappearance of all target lesions, and partial response (PR) was defined as a decrease of at least 30% in the sum of the diameters of the target lesions. Progressive disease (PD) was defined as an increase of at least 20% in the sum of the diameters of the target lesions, or the appearance of one or more new lesions. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Adverse events were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) ver 4.0. Eight out of 78 patients were excluded from this analysis, since only non-measurable lesions, such as bone or lymph node metastasis with ≥ 10 to < 15 mm short axis, existed in these patients.

Risk factors

There are no universal risk factors for patients with metastatic urothelial cancer; however, Eastern Cooperative Oncology Group performance status (PS) more than 0, hemoglobin level less than 10 g/dL, the presence of liver metastasis, and shorter time from prior chemotherapy were included as risk factors in the previous reports by Bellmunt et al. [6, 16] and Sonpavde et al. [15]. We classified the patients according to the number of risk factors as 0, 1 or 2, or more.

Statistical analysis

The OS and PFS curves were analyzed using the Kaplan–Meier method, and the significance of differences between curves was tested using the log-rank test. To assess the prognostic factors which affect survival outcomes, we

also conducted analyses on the baseline characteristics of the patients. A two-sided p value of < 0.05 was considered to be statistically significant. Statistical analysis was carried out using GraphPad Prism ver 7.

Results

Between September 2002 and December 2017, a total of 78 patients received either GD or GP treatment as second-line chemotherapy for advanced or metastatic UC. Characteristics for all patients are shown in Table 1 and correspond to patient status at the start of GD or GP treatment. Of the 78 patients enrolled in this study, 70 could be evaluated to determine treatment efficacy. The median number of cycles of treatment was 2 (range 1–13). Patient responses to treatment are listed in Table 2. One patient (1.4%) had CR, 5 patients (7.1%) had PR, and objective response rate (ORR) was 8.6% (6/70). The median PFS and OS in the total population were 3.5 (95% CI 0.6–53.3) and 9.6 months (95% CI 1.2–53.3), respectively (Fig. 1). No significant difference was observed in the number of risk factors between GP and GD treatment groups (Supplemental Table 1). The median OS of GD and GP was 9.4 (95% CI 0.6–37.0) and 9.8 (95% CI 1.2–53.3) months, respectively. There was no significant difference between the two regimens regarding response parameters (CR, PR, SD or PD) and survival outcomes.

Table 1 Patients' charactersitics

Characteristics	*n*
Median age, years (range)	70 (42–83)
Gender (%)	
Male	57 (73.1%)
Female	21 (26.9%)
ECOG performance status (%)	
0	61 (78.2%)
1	17 (21.8%)
Current or former smoker (%)	38 (48.7%)
First line chemotherapy regimen (%)	
MVAC	2 (3%)
MEC	18 (23%)
GC	58 (74%)
Context of the most recent therapy received	
Neoadjuvant	17 (21.8%)
Adjuvant	21 (26.9%)
First line chemotherapy for metastatic disease	40 (51.3%)
Median time from prior chemotherapy, mo (range)	2 (0–25)
Bladder/Upper urinary tract	33/45
Pure transitional cell future (%)	60 (76.9%)
Visceral disease (%)	45 (57.7%)
Liver metastases (%)	15 (19.2%)
Hb < 10 g/dl (%)	16 (20.5%)
Median number of cycles of first line chemotherapy (range)	2 (1–8)
Median number of cycles of second line chemotherapy (range)	2 (1–13)

ECOG-PS Eastern Cooperative Oncology Group Performance Status, *M-VAC* methotrexate, vinblastine, doxorubicin, and cisplatin, *MEC* methotrexate, epirubicin, and cisplatin, *GC* gemcitabine and cisplatin

Table 2 Best response

	No. of patients (%)			
	All	GP	GD	
CR	1 (1.4)	1 (3.0)	0 (0)	
PR	5 (7.1)	3 (9.1)	2 (5.4)	
SD	32 (45.7)	15 (45.5)	17 (45.9)	
PD	32 (45.7)	14 (42.4)	18 (48.6)	
Total	70	33	37	
ORR	6 (8.6)	4 (12.1)	2 (5.4)	Ns
DCR*	38 (54.3)	19 (57.6)	19 (51.3)	Ns

GP gemcitabine and paclitaxel, *GD* gemcitabine and docetaxel, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

*DCR; CR + PR + SD

Prognostic factors

Analyses on the baseline characteristics of the patients were performed to assess the prognostic factors which affect the survival outcomes. Results are shown in Table 3.

Site of metastases

OS in patients with hepatic or visceral metastasis [5.7 (95% CI, 1.6–16.2) vs. 2.3 (95% CI, 0.6–40.2)] was significantly shorter than that in those without hepatic or visceral metastasis [10.3 (95% CI, 1.6–53.3) vs. 15.0 (95% CI, 2.6–53.3)].

Baseline characteristics

There was no significant difference between the primary sites (bladder or upper urinary tract, $p = 0.4186$) or the level of Eastern Cooperative Oncology Group Performance Status (ECOG-PS) (0 vs. 1, $p = 0.1362$). OS was not affected by either the neutrophil to lymphocyte ratio (NLR) or time from completion or discontinuation of the previous chemotherapy regimen ($p = 0.9476$ and 0.3556, respectively). However, those with anemia (Hb < 10) had significantly shorter OS than those who did not [4.6 (95% CI 0.6–15.6) vs. 12.0 (95% CI 1.6–53.3) months, respectively; $p < 0.0001$]. Risk factors included ECOG performance status above 0, the presence of liver metastasis, Hb < 10 g/dl, and a time, since the completion or discontinuation of the previous therapy of less

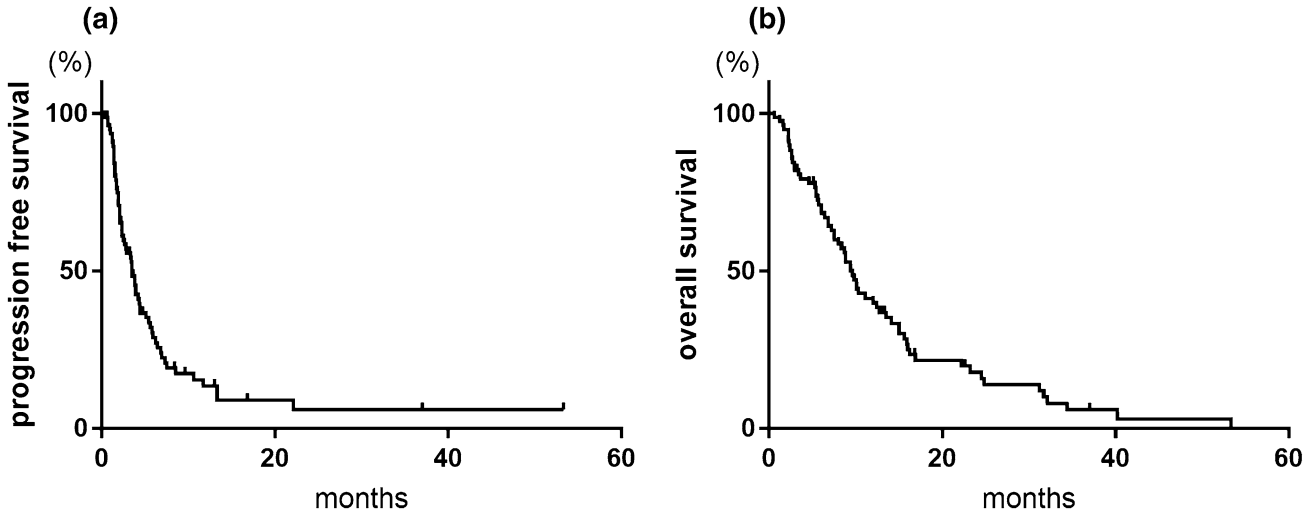

Fig. 1 Progression-free survival (**a**) and overall survival (**b**) of the patients who were treated with second-line chemotherapy (GP or GD) for advanced or metastatic urothelial carcinoma

Table 3 Analyses for association of overall survival

Parameter	HR	*p* value
Age, < 60 vs. ≥ 60	1.25 (0.7478–2.089)	0.5282
Gender, male vs. female	0.9167 (0.5324–1.578)	0.4131
Primary surgery, yes vs. no	1.119 (0.6878–1.821)	0.1836
Primary site, bladder vs. upper urinary tract	1.22 (0.7371–2.02)	0.4186
Liver metastasis, yes vs. no	2.252 (1.001–5.065)	0.0118
Visceral metastasis, yes vs. no	2.188 (1.338–3.58)	0.0012
ECOG performance status, 1 vs. 0	1.519 (0.8032–2.872)	0.1362
Hb, < 10 vs. ≥ 10 g/dl	3.001 (1.25–7.202)	< 0.0001
Time from prior chemotherapy, < 3 vs. ≥ 3 months	1.265 (0.7619–2.099)	0.3556
GP vs. GD	0.9303 (0.5718–1.513)	0.7646
NLR, > 2.5 vs. ≤ 2.5	1.025 (0.486–2.163)	0.9476
No. of risk factors, ≥ 2 vs. 0 or 1	2.496 (1.195–5.215)	0.0006

Risk factors; Hb < 10 g/dl, ECOG performance status above 0, the presence of liver metastasis, a time since the completion or discontinuation of the previous therapy of less than 3 months

GP gemcitabine and paclitaxel, *GD* gemcitabine and docetaxel, *NLR* neutrophil to lymphocyte ratio

than 3 months [15, 16]. A Kaplan–Meier curve of the OS in patients according to the risk factors is shown in Fig. 2. The OS in patients with two or more risk factors was significantly worse than that in those with one or no risk factors (Table 3).

Treatment-related adverse events

Treatment-related toxicities are listed in Table 4. Toxicities were mainly hematological, and the most frequent grade 3–4 toxicities were anemia [$n = 22$ (28.2%)], thrombocytopenia [$n = 29$ (37.2%)], and neutropenia [$n = 55$ (70.5%)], with 3 (3.8%) episodes of febrile neutropenia. A treatment-related death occurred in one patient who received GP therapy. Non-hematological toxicities were mild, and included neuropathy [$n = 14$ (17.9%)] and liver dysfunction [$n = 26$ (33.3%)]. Neutropenia was more frequently observed in GD-treated patients ($p = 0.0407$), but the incidence of neuropathy was significantly higher in GP-treated patients ($p = 0.0023$).

Discussion

In the present study, we reported the outcomes of combination chemotherapy using GP or GD as a second-line treatment in patients with metastatic UC. Both regimens achieved similar OS with tolerable toxicities observed in the majority of patients.

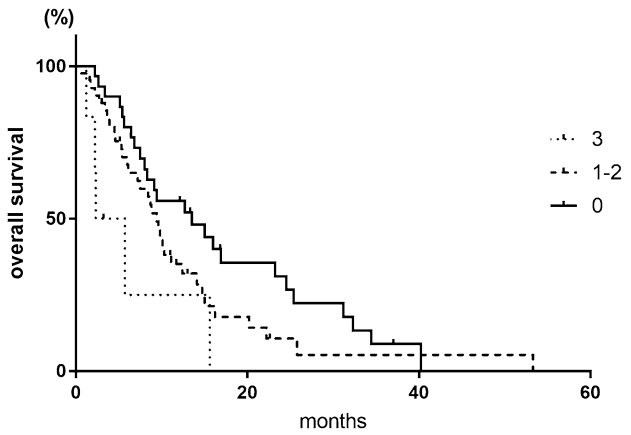

Fig. 2 Risk group classification in the patients with metastatic urothelial carcinoma

Several studies have shown treatment effects of GP combination therapy in a second-line setting for the treatment of advanced or metastatic UC after platinum-based chemotherapy. However, the responses to treatment have been variable [17–21]. There are a number of different factors that may explain these differences. One possible explanation is differences in the doses of gemcitabine and paclitaxel. In a previous study by Fechner et al., the dose of paclitaxel and gemcitabine was 120 and 1250 mg/m^2, respectively, and the median OS was 9 months, which is relatively shorter than in other studies. In the present study, we used 200 mg/m^2 of paclitaxel and 1000 mg/m^2 of gemcitabine. Another explanation is that the proportion of visceral metastasis depended on the reports.

Docetaxel is an active single agent for treating UC patients who were previously treated with first-line chemotherapy. In a phase 2 study of docetaxel therapy for patients with metastatic UC who failed to respond to or relapsed after one prior cisplatin-containing regimen, the median OS was 9 months (95% CI 6–12) [22]. Kim et al. also reported the results from a phase 2 study in which weekly docetaxel as second-line chemotherapy was administered to patients with metastatic UC. Docetaxel (30 mg/m^2) was administered on days 1 and 8 every 21 days, and the median OS was 8.3 months (95% CI 5.9–10.6) [23]. Recently, there have been several reports on docetaxel-based chemotherapy regimens in a second-line setting [7, 14, 24]. Kakutani et al. reported the outcome of docetaxel, ifosfamide and cisplatin chemotherapy with a median OS of 8.5 months (95% CI 6.5–18.8 months) [25]. Furthermore, combination of ramucirumab, a human IgG1 VEGFR-2 antagonist, with docetaxel treatment demonstrated superior PFS period over chemotherapy in patients with platinum-refractory metastatic UC [26]. Although ramucirumab has not yet been approved for the treatment of metastatic UC in Japan, this positive result is likely to permit its approval. Therefore, the combination of ramucirumab and docetaxel could become an important option for second-line therapy, or even third-line therapy after pembrolizumab [27].

The roles of doublet or triplet combinations remain unproven, given the activity of various single agents in the salvage setting. However, combination chemotherapy exhibited improved OS compared with patients enrolled in trials of single-agent chemotherapy as salvage therapy which is reported to be associated with greater toxicity [12]. In this study, incidences of hematological adverse events were higher than those in the previous reports. However, neutropenia was easily managed with granulocyte growth factors, and none of the patients needed routine granulocyte-colony stimulating factor. No patients had severe neuropathy.

In this study, liver and visceral metastasis were experienced in 19.2 and 57.5% of patients, respectively, which is relatively higher than in the previous reports [14, 28]. In the present study, the ORR (8.6%) and median PFS (3.5 months)

Table 4 Adverse events

	No. pf patients (%)				
	GP ($n=37$)		GD ($n=41$)		p value
Adverse event	Any grade	Grade ≧ 3	Any grade	Grade ≧ 3	
Hematological					
Neutropenia	29 (78.4)	22 (59.5)	39 (95.1)	33 (80.5)	0.0407
Anemia	18 (48.6)	4 (10.8)	28 (68.3)	18 (43.9)	Ns
Thrombocytopenia	21 (56.8)	11 (29.7)	31 (75.6)	18 (43.9)	Ns
Non-hematological					
Neuropathy	12 (32.4)	0 (0)	2 (4.9)	0 (0)	0.0023
Gastritis	6 (16.2)	1 (2.7)	9 (22.0)	0 (0)	Ns
Liver dysfunction	10 (27.0)	1 (2.7)	14 (34.1)	1 (2.4)	Ns
Pneumonitis	2 (5.4)	0 (0)	0 (0)	0 (0)	Ns

GP gemcitabine and paclitaxel, *GD* gemcitabine and docetaxel

were modest, but combination chemotherapy yielded favorable outcomes when considering the relatively longer OS (9.6 months) and manageable adverse events.

The present study had several limitations. First, this study was retrospectively designed to compare the two different regimens. Secondly, the cohort was relatively small and it was a single-group study. However, despite the small cohort size, this study was able to show favorable outcomes of second-line chemotherapy treatment using either GD or GP.

In a KEYNOTE-045 trial, pembrolizumab was associated with significantly longer overall survival as second-line therapy for platinum-refractory advanced UC, and has been approved for the treatment of patients with UC who failed to respond to platinum-based chemotherapy [6]. In this trial, pembrolizumab was compared with single-agent chemotherapy with paclitaxel, docetaxel, or vinflunine, and with regard to OS, treatment with pembrolizumab yielded almost 3 months elongation over single-agent chemotherapy (10.3 vs. 7.4 months). Although there have been no randomized trials to compare the survival benefit between combination chemotherapy and checkpoint inhibitors for metastatic UC patients, pembrolizumab has become the gold standard as a second-line therapy for metastatic UC. However, combination chemotherapy could become a third-line therapy after the failure of checkpoint inhibitors.

Conclusions

Both GD and GP were well-tolerated and effective regimens for patients with advanced or metastatic UC that progressed after platinum-based chemotherapy.

Compliance with ethical standards

Conflict of interest All authors declared that they have no conflict of interest.

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