Table 3. Objective response (OR) to paclitaxel, ifosfamide, and nedaplatin (TIN) as second-line chemotherapy in 45 patients with metastatic urothelial carcinoma, stratified by response to first-line chemotherapy

Response to first-line chemotherapy	Response to TIN			
	n	CR (%)	PR (%)	OR (%)
CR	2	1 (50.0)	1 (50.0)	2 (100.0)
PR	6	0 (0.0)	4 (66.7)	4 (66.7)
SD	12	0 (0.0)	2 (16.7)	2 (16.7)
PD	12	0 (0.0)	4 (33.3)	4 (33.3)
NE	13	1 (7.7)	5 (38.5)	6 (46.2)
Total	45	2 (4.4)	16 (35.6)	18 (40.0)

CR, complete response; NE, not evaluable (neoadjuvant or adjuvant chemotherapy); PD, progressive disease; PR, partial response; SD, stable disease.

Table 4. Objective response (OR) to paclitaxel, ifosfamide, and nedaplatin (TIN) as second-line chemotherapy in 45 patients with metastatic urothelial carcinoma, stratified by disease sites

Disease site	Response to TIN			
	n	CR (%)	PR (%)	OR (%)
Multiple organs	19	1 (5.3)	3 (15.8)	4 (21.1)
Lymph nodes	19	1 (5.3)	9 (47.4)	10 (52.6)
Lung	4	0 (0.0)	3 (75.0)	3 (75.0)
Duodenum	1	0 (0.0)	0 (0.0)	0 (0.0)
Ovary	1	0 (0.0)	0 (0.0)	0 (0.0)
Local	1	0 (0.0)	1 (100.0)	1 (100.0)
Total	45	2 (4.4)	16 (35.6)	18 (40.0)

CR, complete response; PR, partial response.

patients with MUC. The median OS was 42 months for patients who underwent postchemotherapy surgery, which was significantly longer than that for patients without surgery (10 months).[26] In contrast, Otto *et al.*[27] reported that surgical resection had no impact on survival but only on the quality of life of patients with symptomatic disease. This study showed that patients with a small number of metastatic sites who underwent salvage resection had more favorable survival. Although there is a limitation because of the small number of patients in this study, properly selected patients may be considered for consolidation surgery.

Table 5. Toxicity profile of 45 patients who underwent treatment with paclitaxel, ifosfamide, and nedaplatin as second-line chemotherapy for metastatic urothelial carcinoma

Toxicity	Grade (all cycles), no. of patients (%)			
	1	2	3	4
Hematologic				
Leukopenia	0 (0)	2 (4.4)	21 (46.7)	21 (46.7)
Neutropenia	0 (0)	1 (2.2)	2 (4.4)	41 (91.1)
Thrombocytopenia	10 (22.2)	10 (22.2)	5 (11.1)	3 (6.7)
Anemia	10 (22.2)	14 (31.1)	7 (15.6)	0 (0.0)
Febrile neutropenia			10 (22.2)	
Non-hematologic				
Anorexia	12 (26.7)	13 (28.9)	2 (4.4)	0 (0.0)
Vomiting	3 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral neuropathy	0 (0.0)	7 (15.6)	0 (0.0)	0 (0.0)
AST/ALT, elevated	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)
Creatinine, elevated	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)
Alopecia	0 (0.0)	45 (100.0)	0 (0.0)	0 (0.0)

Toxic effects were graded in agreement with National Cancer Institute Common Toxicity Criteria, version 3.0. ALT, alanine transaminase; AST, aspartate transaminase.

The main limitation of this study is that only 10 patients (22.2%) who were previously treated with GC were included. Recently, more patients with MUC undergo GC rather than MVAC as their first-line chemotherapy because of the anticancer activity and lower toxicity of GC, which means that there are fewer gemcitabine-naïve patients at the time of second-line chemotherapy. Although paclitaxel/gemcitabine is hematologically less toxic than TIN, a regimen other than gemcitabine should be considered. Further studies are needed including more GC-failure patients.

In conclusion, TIN therapy is a tolerable and active regimen for treating MUC after MVAC or GC failure. We suggest that TIN can be one of the options for second-line chemotherapy for MUC patients in the GC era. Salvage surgery can be offered to patients with a good response to TIN, which may provide longer survival.

Disclosure Statement

The authors have no conflict of interest.

References

1 Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009; **59**: 225–49.
2 Vaishampayan U. Systemic therapy of advanced urothelial cancer. *Curr Treat Options Oncol* 2009; **10**: 256–66.
3 Sternberg CN, Yagoda A, Scher HI *et al.* Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. *Cancer* 1989; **64**: 2448–58.
4 Loehrer PJ Sr, Einhorn LH, Elson PJ *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**: 1066–73.
5 von der Maase H, Sengelov L, Roberts JT *et al.* 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**: 4602–8.
6 Stenzl A, Cowan NC, De Santis M *et al.* The updated EAU guidelines on muscle-invasive and metastatic bladder cancer. *Eur Urol* 2009; **55**: 815–25.
7 Bachner M, De Santis M. Second-line therapy in bladder cancer. *Curr Opin Urol* 2009; **19**: 533–9.
8 Matsumoto K, Irie A, Satoh T, Okazaki M, Iwamura M, Baba S. Gemcitabine and paclitaxel chemotherapy as a second-line treatment for advanced or metastatic urothelial carcinoma. *Int J Urol* 2007; **14**: 1000–4; discussion 4.
9 Kanai K, Kikuchi E, Ohigashi T *et al.* Gemcitabine and paclitaxel chemotherapy for advanced urothelial carcinoma in patients who have received prior cisplatin-based chemotherapy. *Int J Clin Oncol* 2008; **13**: 510–4.
10 Suyama T, Ueda T, Fukasawa S *et al.* Combination of gemcitabine and paclitaxel as second-line chemotherapy for advanced urothelial carcinoma. *Jpn J Clin Oncol* 2009; **39**: 244–50.
11 Kouno T, Ando M, Yonemori K *et al.* Weekly paclitaxel and carboplatin against advanced transitional cell cancer after failure of a platinum-based regimen. *Eur Urol* 2007; **52**: 1115–22.
12 Sweeney CJ, Williams SD, Finch DE *et al.* A Phase II study of paclitaxel and ifosfamide for patients with advanced refractory carcinoma of the urothelium. *Cancer* 1999; **86**: 514–8.
13 Pectasides D, Aravantinos G, Kalofonos H *et al.* Combination chemotherapy with gemcitabine and ifosfamide as second-line treatment in metastatic urothelial cancer. A phase II trial conducted by the Hellenic Cooperative Oncology Group. *Ann Oncol* 2001; **12**: 1417–22.
14 Lin CC, Hsu CH, Huang CY *et al.* Gemcitabine and ifosfamide as a second-line treatment for cisplatin-refractory metastatic urothelial carcinoma: a phase II study. *Anticancer Drugs* 2007; **18**: 487–91.

doi: 10.1111/j.1349-7006.2011.01909.x

15 Tu SM, Hossan E, Amato R, Kilbourn R, Logothetis CJ. Paclitaxel, cisplatin and methotrexate combination chemotherapy is active in the treatment of refractory urothelial malignancies. *J Urol* 1995; **154**: 1719–22.
16 Pagliaro LC, Millikan RE, Tu SM *et al.* Cisplatin, gemcitabine, and ifosfamide as weekly therapy: a feasibility and phase II study of salvage treatment for advanced transitional-cell carcinoma. *J Clin Oncol* 2002; **20**: 2965–70.
17 Shinohara N, Harabayashi T, Suzuki S *et al.* Salvage chemotherapy with paclitaxel, ifosfamide, and nedaplatin in patients with urothelial cancer who had received prior cisplatin-based therapy. *Cancer Chemother Pharmacol* 2006; **58**: 402–7.
18 Nakaigawa N, Miyoshi Y, Hattori Y *et al.* Chemotherapy based on a chemosensitivity test in urothelial cancer. *Urol View (in Japanese)* 2008; **6**: 109–15.
19 Furukawa T, Kubota T, Hoffman RM. Clinical applications of the histoculture drug response assay. *Clin Cancer Res* 1995; **1**: 305–11.
20 Desoize B, Madoulet C. Particular aspects of platinum compounds used at present in cancer treatment. *Crit Rev Oncol Hematol* 2002; **42**: 317–25.
21 Therasse P, Arbuck SG, Eisenhauer EA *et al.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**: 205–16.
22 Green SJ, Dahlberg S. Planned versus attained design in phase II clinical trials. *Stat Med* 1992; **11**: 853–62.
23 Bajorin DF, McCaffrey JA, Dodd PM *et al.* Ifosfamide, paclitaxel, and cisplatin for patients with advanced transitional cell carcinoma of the urothelial tract: final report of a phase II trial evaluating two dosing schedules. *Cancer* 2000; **88**: 1671–8.
24 Cao W, Xu C, Lou G *et al.* A phase II study of paclitaxel and nedaplatin as first-line chemotherapy in patients with advanced esophageal cancer. *Jpn J Clin Oncol* 2009; **39**: 582–7.
25 Dodd PM, McCaffrey JA, Herr H *et al.* Outcome of postchemotherapy surgery after treatment with methotrexate, vinblastine, doxorubicin, and cisplatin in patients with unresectable or metastatic transitional cell carcinoma. *J Clin Oncol* 1999; **17**: 2546–52.
26 Abe T, Shinohara N, Harabayashi T *et al.* Impact of multimodal treatment on survival in patients with metastatic urothelial cancer. *Eur Urol* 2007; **52**: 1106–13.
27 Otto T, Krege S, Suhr J, Rubben H. Impact of surgical resection of bladder cancer metastases refractory to systemic therapy on performance score: a phase II trial. *Urology* 2001; **57**: 55–9.

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ORIGINAL ARTICLE

Combination therapy consisting of gemcitabine, carboplatin, and docetaxel as an active treatment for advanced urothelial carcinoma

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Abstract
Background To evaluate the efficacy and toxicity of a combination chemotherapy consisting of gemcitabine, carboplatin, and docetaxel (GCD) in patients with advanced urothelial carcinoma (UC) as a phase II trial.
Materials and methods Patients with metastatic or locally advanced unresectable UC were eligible for this trial. All enrolled patients were considered to be "unfit" for cisplatin-based chemotherapy, or to have methotrexate, vinblastine, doxorubicin, cisplatin (MVAC)-refractory UC. The chemotherapy regimen consisted of gemcitabine 1000 mg/m^2 on days 1 and 8, and carboplatin (with a target area under the curve of 5) and docetaxel 70 mg/m^2 on day 1; this was repeated every 21 days.
Results Thirty-five patients were enrolled, with a median age of 68 years. A total of 89 cycles were administered (median, 2 cycles). Major toxicities were Grade 3/4 neutropenia in 28 (80.0%) patients and Grade 3/4 thrombocytopenia in 18 (51.5%). An objective response rate (ORR) was 11 of 21 patients (52.4%), including a complete response in 1 (4.8%). The median overall survival (OS) was 13.1 months (1-year survival rate, 60%) and the median progression-free survival (PFS) was 5.0 months. Among 16 patients who had previously received MVAC, the ORR, the median PFS, the median OS and 1-year survival rate was 56.3%, 5.0 months, 12.6 months and 54%, respectively.
Conclusions GCD chemotherapy is active and well tolerated as a first- or second-line therapy for patients with advanced UC. Response rate, duration and survival did not differ between those with and without a history of MVAC treatment.

Keywords Gemcitabine · Carboplatin · Docetaxel · Advanced urothelial carcinoma · Second-line chemotherapy

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Introduction

In the 1990s, the most common first-line systemic chemotherapy for patients with advanced and/or unresectable urothelial carcinoma (UC) was combination therapy with cisplatin, methotrexate, doxorubicin, and vinblastine (MVAC) [1]. In Phase III studies of MVAC therapy in patients with advanced UC, the objective response rate (ORR) was 35–45%, and the median overall survival (OS) was 12 months [1, 2]. Although the frequency of response to MVAC therapy was promising, the duration of response was short, and the survival rate at 5 years after initiating the therapy was only 3.2%. In addition, treatment with MVAC is associated with substantial toxicity, including myelosuppression, mucositis, nephrotoxicity, and neuropathy. Therapy-related mortality rates range from 2 to 4% [2, 3]. Recently, Phase II and Phase III studies found that gemcitabine–cisplatin (GC) combination therapy was effective and comparable to MVAC in the treatment of patients with advanced UC [4, 5]. Compared with MVAC therapy, the safety profile of GC therapy was better and the ORR was similar (49 and 46% for GC therapy and MVAC, respectively). However, the therapeutic application of GC to patients with renal impairment is difficult because of the

renal toxicity of cisplatin. Since the impairment of renal function is common in patients with advanced UC, it is necessary to develop more active and less toxic treatments.

Carboplatin was developed with the intent of providing an efficacy that is similar to that of cisplatin and has less renal toxicity. Carboplatin seldom causes renal impairment and has an established formula (Calvert formula) that allows for the accurate dosing of the drug on the basis of renal function. The latter has made this agent an attractive alternative to cisplatin.

Docetaxel is also an active single agent in previously-treated patients with UC. In a Phase II study of docetaxel therapy in patients with advanced or metastatic UC relapsing or refractory to no more than one prior cisplatin-containing treatment regimen, the ORR rate was 13.3%, and the median OS was 9 months [6]. Furthermore, docetaxel and gemcitabine combination therapy has also been reported to be active and well tolerated in elderly patients with advanced non-small-cell lung cancer [7, 8].

Our study was designed to evaluate the safety and efficacy of combination chemotherapy consisting of gemcitabine, carboplatin, and docetaxel (GCD) in patients with metastatic and/or locally advanced unresectable UC who had previously undergone MVAC chemotherapy or were not suitable for cisplatin therapy.

Materials and methods

Patients

Thirty-five patients who were treated between April 2002 and March 2008 at the Akita University Hospital were enrolled in this study. All of them had histologically confirmed UC that was either metastatic or locally advanced and unresectable. In addition, patients eligible for this study had to meet at least one of the following three criteria: (1) Patients were considered to be "unfit" for administration of cisplatin [e.g., MVAC, high-dose-intensity MVAC (HD-MVAC)] because of advanced age and/or renal dysfunction (serum creatinine greater than 1.2 mg/dL). (2) Patients had had to discontinue first-line chemotherapy with MVAC or HD-MVAC because of tumor progression or unacceptable toxicity. (3) The disease had relapsed in patients after first-line chemotherapy with MVAC or HD-MVAC. Prior cytotoxic treatment and local radiation were permitted. Eastern Cooperative Oncology Group (ECOG) performance scores were 0, 1, or 2 for all patients. Patients should have recovered from any effects of a major surgery, and at least 4 weeks should have elapsed since completion of chemotherapy. Written informed consent was obtained in all cases. The study was approved by the institutional ethical review board of Akita University Graduate School of Medicine.

Treatment plan

Table 1 outlines the treatment schedule and dose of the GCD regimen. Docetaxel infusion preceded the infusion of carboplatin, which was infused on day 1. The carboplatin infusion was followed by gemcitabine infusion. The starting dose level (level 0) was maintained in patients whose neutrophil count at the nadir was 500/mm^3 or greater, and whose platelet count at the nadir was 50,000/mm^3 or greater. In patients with a neutrophil nadir of <500/mm^3 and/or a platelet count nadir <50,000/mm^3, the dose was reduced by one dose level for the next cycle. If the neutrophil nadir was less than 500/mm^3, or if the platelet count nadir was less than 50,000/mm^3 after a reduction in dose level (−1), then subsequent cycles were started at a lower dose level (−2). Gemcitabine was administered at day 8 only if the neutrophil count was 1000/mm^3 or greater and if the platelet count was 100,000/mm^3 or greater. The dose could not be escalated once it was reduced.

Assessment of response and adverse events

Radiographic analyses of tumor size and tumor burden, and disease staging were performed at baseline and after every second cycle, or as indicated clinically. Responses to GCD combination therapy were determined using the definitions according to RECIST version 1.0 [9]. The duration of response was determined from the date of the observed response to the date of disease progression, or the last contact with the patient. Survival duration was measured from the initiation of the first cycle of GCD chemotherapy until death or the last contact with the patient.

The severity of adverse events was graded according to NCI-CTCAE version 2.0.

Statistical analysis

OS and progression-free survival (PFS) were plotted by the Kaplan–Meier method, and differences between groups were calculated by the log-rank test. Comparison of response rate between groups was performed using Fisher's exact test. Statistical analysis was carried out using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

Table 1 Treatment plan (21-day cycle)

Agent	Days	Full dosage	Dose reduction 1	Dose reduction 2
Gemcitabine (mg/m^2)	1, 8	1000	800	600
Carboplatin (AUC)	1	5	4	3
Docetaxel (mg/m^2)	1	70	60	50

Results

Patients characteristics

From April 2002 to March 2008, 35 patients were enrolled in this study. A total of 14 patients were treated with radiation combination therapy. Demographic and baseline characteristics of the patients are presented in Table 2. The median age was 68 years (range 41–83 years). ECOG performance status was 0 in 30 of 35 patients (85.7%), and 1 in the other 5 patients (14.3%). Twenty-six patients (74.3%) had previously undergone chemotherapy (neoadjuvant and/or adjuvant chemotherapy), which included HD-MVAC in 24 patients, and MVAC in 2 patients. Twelve patients had prior total cystectomy, and 7 patients had prior nephro-ureterectomy. Metastasis to at least 1 region outside of the urothelial tract was observed in all 35 patients (100.0%). The most frequent site of metastasis was the lymph nodes (17 of 35 patients; 43.6%).

Table 2 Patient characteristics

Characteristic	No. of patients (%)
Total	35 (100)
Age (years)	
Median	68
Range	41–83
Gender	
Female	6 (17.1)
Male	29 (82.9)
ECOG performance status	
0	30 (85.7)
1	5 (14.3)
2	0 (0.0)
Serum creatinine	
≥1.2	11 (31.4)
<1.2	24 (68.6)
Prior chemotherapy	
HD-MVAC	24 (68.6)
MVAC	2 (5.7)
None	9 (25.7)
Site of disease	
Locoregionally advanced	
Upper urinary tract	9 (25.7)
Bladder	4 (11.4)
Recurrent or metastatic	
Lymph node	17 (48.6)
Lung	9 (25.7)
Liver	7 (20.0)
Soft tissue	4 (11.4)
Bone	4 (11.4)
Pelvis	1 (2.9)
No. of target organs per patients	
1	22 (62.9)
2	7 (20.0)
≥3	6 (17.1)

Treatment administered

All the 35 patients received a total of 89 cycles of chemotherapy (median of 2 cycles; range 1–8 cycles). No dose reductions were required in 13 of 26 patients (50.0%) at the beginning of the 2nd cycle.

Adverse effects

The overall safety of the treatment regimen was evaluated according to the frequency and severity of treatment-related adverse events. Frequencies of Grade 1 to Grade 4 adverse events are shown in Table 3. Neutropenia was the most frequently observed Grade 3/4 adverse event with the GCD regimen. Twenty-eight of 35 patients (80.0%) experienced Grade 3/4 neutropenia. The incidence rate of Grade 3/4 adverse effects in 11 patients with impaired renal function was not different from that in 24 patients with normal renal function. For example, Grade 3/4 neutropenia was noted in 65.7 and 83.3%, and Grade 3/4 anemia in 45.5 and 41.7%, respectively. Similarly, the incidence rate of Grade 3/4 adverse effects in patients over 75 years was not different from that in patients aged 75 years or younger. For example, Grade 3/4 neutropenia was observed in 77.7 and 77.0%, and Grade 3/4 anemia in 33.3 and 46.2%, respectively. No toxicity-related deaths were encountered in this phase II study.

Tumor response

A total of 35 patients could be assessed for response. Excluding the 14 patients who had received combination radiation therapy, the ORR was 52.4% (11 of 21 patients), including a complete response (CR) in 1 (4.8%), and a partial response (PR) in 10 (47.6%). Another 9 patients (42.9%) had stable disease. The response rate (CR + PR) among patients with lymph node, lung, liver, and soft tissue metastases was 41.2, 12.5, 50.0, and 50.0%, respectively. Among 16 patients who had previously received MVAC or HD-MVAC, the ORR was 56.3% (9 patients), including a CR in 1 (6.3%), and a PR in 8 (50.0%). The ORR in patients previously treated with MVAC or HD-MVAC was not different from that in patients without previous chemotherapy ($p = 0.53$).

Table 3 Adverse events

Adverse events	Grade 4	Grade 3	Grade 2	Grade 1
Hematologic				
Neutropenia	14 (40.0)	14 (40.0)	7 (20.0)	0 (0.0)
Thrombocytopenia	1 (2.9)	17 (48.6)	8 (22.9)	8 (22.8)
Anemia	3 (8.6)	12 (34.3)	14 (40.0)	6 (17.1)
Nonhematologic				
Diarrhea	1 (2.9)	6 (17.1)	6 (17.1)	3 (8.6)
Nausea and emesis	1 (2.9)	2 (5.7)	4 (11.4)	6 (17.1)
Anorexia	0 (0.0)	10 (28.6)	7 (20.0)	11 (31.4)
Gastrointestinal bleeding	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)

Values are expressed as no. (%)

Survival

The outcome of GCD combination chemotherapy on overall survival duration (i.e., time from the first treatment with the study drugs to death due to any cause) was determined for the 35 enrolled patients (Fig. 1). Among the 21 patients without combination radiation therapy, the median OS was 13.1 months [95% confidence interval (CI) 11.4–14.7 months], with a 1-year survival of 60%, and a 2-year survival of 24%. The median PFS was 5.0 months (95% CI 2.3–7.7 months). In the 16 patients who had previously received MVAC or HD-MVAC, the median OS was 12.6 months (95% CI 8.9–16.3 months), with a 1-year survival rate of 54%, and a 2-year survival rate of 22% (Fig. 2). The median PFS was 5.0 months (95% CI 3.2–6.8 months) (Fig. 3).

Finally, the OS in patients who had previously been treated with MVAC or HD-MVAC was not different from that of patients without such a history ($p = 0.13$).

Discussion

Despite significant progress with combination chemotherapy, advanced UC remains a fatal disease for the vast majority of patients with metastatic or unresectable disease. The two active agents—paclitaxel and gemcitabine—have been reported to have favorable toxicity profiles and a potentially synergistic interaction with platinum [10, 11]. Therefore, these two drugs have led to the development of taxane- and gemcitabine-based doublets with cisplatin or carboplatin [12–15]. Although GC combination chemotherapy appears to be well tolerated, the complete response rate and survival with this combination is not superior to that of MVAC, and the response duration is short [16]. Furthermore, patients with advanced UC are often considered to be "unfit" for cisplatin-based chemotherapy because they are often at an advanced age, and have

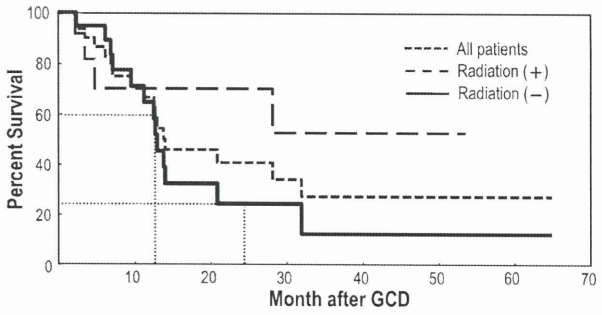

Fig. 1 The OS for all patients with unresectable metastatic or locally advanced UC ($n = 35$)

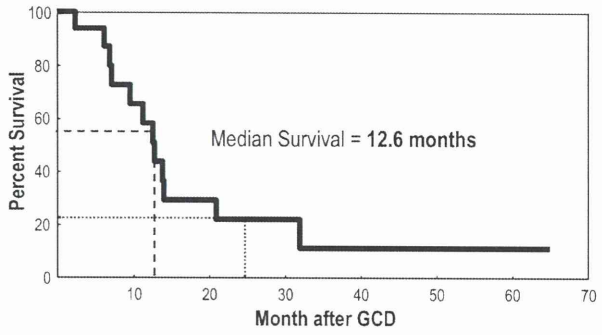

Fig. 2 The OS for patients who were previously treated with MVAC or HD-MVAC chemotherapy for metastatic UC. The patients who received concomitant radiation therapy were excluded from this analysis

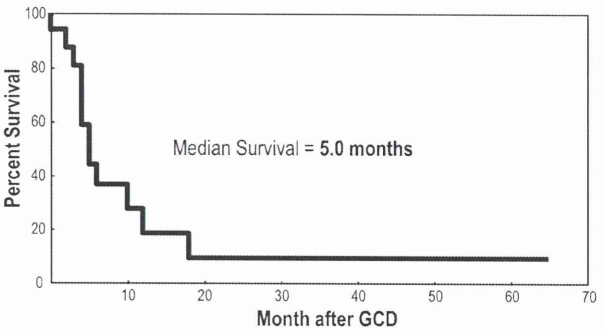

Fig. 3 The PFS among patients who were previously treated with MVAC or HD-MVAC chemotherapy for metastatic UC

impaired renal function (although judgements to this effect and the criteria for "unfit" may often be based on the physician's discretion or preference). We sought to enhance the treatment efficacy by developing regimens incorporating three active agents to build on taxan- and gemcitabine-based chemotherapy [16, 17], while reducing toxicity by the application of carboplatin.

With a median of two courses, the present GCD chemotherapy was well tolerated despite the fact that a number of patients were elderly (mean 68 years), and 26% were

over 75 years in age. While Grade 3/4 myelosuppression was often encountered, the frequencies of hematologic toxicity were similar to those seen with GC combination chemotherapy [5]. In spite of the high incidence of Grade 3/4 toxicity, there was no drug toxicity-related death. Furthermore, the incidence rate of Grade 3/4 adverse effects was not distinctively high in elderly patients, or in patients with impaired renal function. Therefore, we believe that the GCD regimen was well tolerated and safe, even in elderly patients and those with impaired renal function.

In the present study, the ORR was 52.4%, with a CR rate of 4.8%. The response rate in this study was relatively lower than that of the paclitaxel–carboplatin–gemcitabine combination therapy reported by Hussain et al. (52.4 vs. 68%) [16]. One possible reason for this difference in response rate was that our study included a larger number of patients with a previous history of chemotherapy with MVAC or HD-MVAC (60 vs. 11% in the study by Hussain et al. [16]). On the other hand, the median OS was 13.1 months in our study; this result is similar to that reported with GC combination therapy (12–14 months) [4, 15, 18] and MVAC combination therapy (12 months) [19, 20]. It is notable that in all of the reported studies the patients were chemo-naive. Considering that the present study included 26 (74.3%) patients who had a previous history of chemotherapy with MVAC or HD-MVAC, the GCD regimen appears to be at least as effective as the MVAC or GC regimen. Comparing patients who received radiation therapy with GCD chemotherapy with those who received GCD chemotherapy alone, the patients who received radiation had a better survival rate (Fig. 1). One possible reason for this difference might be the radiosensitization effect of docetaxel and carboplatin; this could also be the reason why the 14 patients (40.0%) who received radiation therapy plus GCD chemotherapy had only 1 target lesion that could be controlled with chemoradiation therapy.

As a second-line chemotherapy for prior MVAC-treated metastatic UC, the results of the present study indicate that the GCD chemotherapy is effective with outcomes that are comparable to those seen in patients without any history of chemotherapy. Of the 16 patients who could be assessed for response to therapy, the ORR was 56.3%, and the median OS was 12.6 months (Figs. 2, 3). Currently, there is no established second-line chemotherapy for patients who experience clinical failure or recurrence after platinum-based chemotherapy, including MVAC and GC. There have been a number of recent reports of clinical trials that have been performed to address this issue [6, 21–28]. McCaffrey et al. [6] described the results of a Phase II trial that used docetaxel monotherapy and showed that the ORR was 13.3%, and the median OS was 5.1 months. Gemcitabine monotherapy has been shown to provide a 22–23% ORR, with 5–9 months median OS, and 3.1–3.8 months median PFS [22, 23]. In trials of paclitaxel plus carboplatin/cisplatin combination therapy, the ORR was 16–36%, the median OS was 6–10.3 months, and the median PFS was 4–6.2 months [15–18]. In trials of gemcitabine plus docetaxel/paclitaxel combination therapy, the ORR was 17–27%, and the median PFS was 7.7–14.4 months [21, 28]. The 53.0% ORR and 13.1 months median OS achieved in our study seems to be comparable with the results reported in these previous reports. Therefore, we believe that our GCD triplet combination may possess substantial activity against advanced UC that has recurred after failure of platinum-containing regimens, especially MVAC and HD-MVAC. However, this remains merely a possibility at present and whether the current GCD regimen is also effective against advanced UC after treatment failure or recurrence following GC chemotherapy should be further investigated. Furthermore, because the duration of PFS in the present study remained rather short at 5 months, the development of a more active and durable regimen requiring the aid of new active agents may be required.

In summary, GCD chemotherapy was effective in patients with advanced UC, even in those with a history of MVAC or HD-MVAC treatment. The regimen was feasible in elderly patients as well as in patients with impaired renal function. However, the short duration of PFS remains a major problem.

Conflict of interest No author has any conflict of interest.

References

1. Saxman SB, Propert KJ, Einhorn LH et al (1997) Long-term follow-up of a Phase III intergroup study of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol 15:2564–2570
2. Stadler WM, Kuzel TM, Rahgavan D et al (1997) Metastatic bladder cancer: advances in therapy. Eur J Cancer 33:523–526
3. Sternberg CN, Yagoda A, Scher HI et al (1989) Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelial: Efficacy and patterns of response and relapse. Cancer 64:2448–2458
4. Kaufman D, Raghavan D, Carducci M et al (2000) Phase II trial of gemcitabine plus cisplatin in patients with metastatic urothelial cancer. J Clin Oncol 18:1921–1927
5. von der Maase VDH, Hansen SW, Roberts JT et al (2000) 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 18:3068–3077
6. MaCafferey JA, Hilton S, Mazumdar M et al (1997) Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. J Clin Oncol 15:1853–1857
7. Hainsworth JD, Erland JB, Barton JH et al (2003) Combination treatment with weekly docetaxel and gemcitabine for advanced

non-small-cell lung cancer in elderly patients and patients with poor performance status: results of Minnie Pearl Cancer Research Network phase II trial. Clin Lung Cancer 5:33–38
8. Hainsworth JD, Spigel DR, Farley C et al (2007) Weekly docetaxel versus docetaxel/gemcitabine in the treatment of elderly or poor performance status patients with advanced nonsmall cell lung cancer. Cancer 110:2027–2034
9. Therasse P, Arbucl SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205–216
10. Jekunen AP, Christen RD, Shalinsky DR et al (1994) Synergistic interaction between cisplatin and taxol in human ovarian carcinoma cell in vitro. Br J Cancer 69:299–306
11. Peters GJ, Bergman AM, Ruiz van Haperen VW et al (1995) Interaction between cisplatin and gemcitabine in vitro and in vivo. Semin Oncol 22:72–79
12. Dreicer R, Monala J, Roth BJ et al (2000) Phase II study of cisplatin and paclitaxel in advanced carcinoma of the urothelium: an Eastern Cooperative Oncology Group Study. J Clin Oncol 18:1058–1061
13. Zielinski CC, Schnack B, Grbovic M et al (1998) Paclitaxel and carboplatin in patients with metastatic urothelial cancer: results of a phase II trial. Br J Cancer 78:370–374
14. Bellmunt J, de Wit R, Albanell J et al (2001) A feasibility study of carboplatin with fixed dose of gemcitabine in 'unfit' patients with advanced bladder cancer. Eur J Cancer 37:2212–2215
15. von der Maase H, Hansen SW, Roberts JT et al (2000) 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 17:3068–3077
16. Hussain M, Vaishampayan U, Du W et al (2001) Combination paclitaxel, carboplatin, and gemcitabine is an active treatment for advanced urothelial cancer. J Clin Oncol 19:2527–2533
17. Hoshi S, Ohyama C, Ono K et al (2004) Gemcitabine plus carboplatin, and gemcitabine, docetaxel and carboplatin combined chemotherapy regimens in patients with metastatic urothelial carcinoma previously treated with a platinum-based regimen. Int J Clin Oncol 9:125–129
18. Moore MJ, Winquist EW, Murray N et al (1999) Gemcitabine plus cisplatin, an active regimen in advanced urothelial cancer: a phase II trial of the national cancer institute of Canada clinical trials group. J Clin Oncol 17:2876–2881
19. Logothetis CJ, Dexeus FH, Finn L et al (1990) A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumors. J Clin Oncol 8:1050–1055
20. Loehrer PJ Sr, Einhorn LH, Elson PJ et al (1992) 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 7:1066–1073
21. Sternberg CN, Calabro F, Pizzocaro G et al (2001) Chemotherapy with an every-2-week regimen of gemcitabine and paclitaxel in patients with transitional cell carcinoma who have received prior cisplatin-based therapy. J Clin Oncol 92:2993–2998
22. Lorusso V, Pollera CF, Autimi M et al (1998) A phase II study of gemcitabine in patients with transitional cell carcinoma of the urinary tract previously treated with platinum. Eur J Cancer 34:1208–1212
23. Akaza H, Naito S, Usami M et al (2007) Efficacy and safety of gemcitabine monotherapy in patients with transitional cell carcinoma after cisplatin-containing therapy: a Japanese experience. Jpn J Clin Oncol 37:201–206
24. Uhm JE, Lim HY, Kim WS et al (2007) Paclitaxel with cisplatin as salvage treatment for patients with previously treated advanced transitional cell carcinoma of the urothelial tract. Neoplasia 9:18–22
25. Kouno T, Ando M, Yonemori K et al (2007) Weekly paclitaxel and carboplatin against advanced transitional cell cancer after failure of a platinum-based regimen. Eur Urol 52:1115–1122
26. Soga N, Onishi T, Arima K et al (2007) Paclitaxel carboplatin chemotherapy as a second-line chemotherapy for advanced platinum resistant urothelial cancer in Japanese cases. Int J Urol 14:828–832
27. Vaishampayan UN, Faulkner JR, Small EJ et al (2005) Phase II trial of carboplatin and paclitaxel in cisplatin-pretreated advanced transitional cell carcinoma. Cancer 104:1627–1632
28. Dreicer R, Manola J, Schneider DJ et al (2003) Phase II trial of gemcitabine and docetaxel in patients with advanced carcinoma of the urothelium. Cancer 97:2743–2747

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Combination of Gemcitabine and Paclitaxel is a Favorable Option for Patients with Advanced or Metastatic Urothelial Carcinoma Previously Treated with Cisplatin-based Chemotherapy

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Objective: To evaluate the efficacy and toxicity of a gemcitabine and paclitaxel regimen for patients with advanced urothelial carcinoma who had previously been treated with methotrexate, vinblastine, doxorubicin and cisplatin chemotherapy, and to determine the prognostic factors for survival in second-line chemotherapy.
Methods: From June 2005 to April 2010, 24 eligible patients who had previously been treated with methotrexate, vinblastine, doxorubicin and cisplatin chemotherapy were enrolled in this study. Patients received paclitaxel 200 mg/m^2 on Day 1 and gemcitabine 1000 mg/m^2 on Days 1, 8 and 15. The gemcitabine and paclitaxel regimen was repeated every 3 weeks. Patients were evaluated every two cycles by imaging study.
Results: Ten of 24 patients (42%) had major response to the gemcitabine and paclitaxel regimen, including 2 patients (8%) who had complete response. Median survival time and median progression-free survival were 12.4 and 6.1 months, respectively. Good performance status and major response to first-line methotrexate, vinblastine, doxorubicin and cisplatin treatment were significant predictors of overall survival and progression-free survival. Grade 3 or 4 neutropenia occurred in 16 patients (67%), but there were no severe infections. There were no treatment-related deaths.
Conclusions: Gemcitabine and paclitaxel chemotherapy had favorable benefit and safety profiles, and the regimen is recommended as a potential second-line chemotherapy for advanced or metastatic urothelial carcinoma previously treated with methotrexate, vinblastine, doxorubicin and cisplatin chemotherapy.

Key words: second-line chemotherapy – gemcitabine – paclitaxel – urothelial carcinoma

INTRODUCTION

Cisplatin-based systemic chemotherapy is the gold standard approach for patients with advanced or metastatic urothelial carcinoma (UC). Combined chemotherapy with methotrexate, vinblastine, doxorubicin and cisplatin (MVAC), which was developed about 25 years ago, is an effective and frequently used modality for these life-threatening diseases (1–5). Recently, combined chemotherapy with gemcitabine and cisplatin (GC) has become another standard treatment for advanced UC (6,7). Overall survival is similar for both regimens, with a median survival of 14.0 months for GC and 15.2 months for MVAC, and 5-year overall survival rates of 13.0 and 15.5%, respectively. However, several limitations remain with MVAC and GC treatment. Long-term follow-up has revealed that overall survival or progression-free survival is poor, particularly with metastatic UC (5,6). Furthermore, there is no standard second-line treatment in patients with UC after the failure of cisplatin-based chemotherapy.

Many combination regimens, including paclitaxel and carboplatin (8–10), gemcitabine and ifosfamide (11,12), gemcitabine and docetaxel (13) and other combination regimens (14,15), have been reported as second-line chemotherapy for advanced UC. These combination regimens have demonstrated an overall response rate of 16–41% and a median survival time of approximately 7 months. Among these chemotherapeutic agents, paclitaxel is an antimitotic spindle drug that promotes microtubular aggregation and interferes with such cellular functions as mitosis cell transport and cell motility. Single agent paclitaxel was shown to have an overall response rate of 42% in previously untreated UC (16). Gemcitabine, an analog of cytarabine, is a pyrimidine antimetabolite. The antitumor effect of gemcitabine is mediated by the inhibition of DNA synthesis. Single agent gemcitabine has demonstrated a response rate of 23–28% (17,18). Furthermore, a gemcitabine and paclitaxel (GP) pharmacokinetic study showed that paclitaxel increased the accumulation of gemcitabine triphosphate, the active metabolite of gemcitabine (19). In previous reports, GP combination therapy showed an overall response rate of 30–69% and a median survival time of approximately 13 months in previously treated and chemo-naïve patients (20–26).

We have previously shown that the GP regimen paired with another antitumor mechanism is effective in patients with advanced or metastatic UC who have previously been treated with MVAC (27). Although the number of patients enrolled was relatively small in the previous study, we updated the analysis of overall response rate and survival and determined the prognostic factors for survival with this second-line chemotherapy.

PATIENTS AND METHODS

Patients

Eligible patients had measurable or assessable tumors which were histologically proved to have locally advanced (T2–T4, N1 or N2) or metastatic (M1) UC of the urinary bladder and upper urinary tract. All patients received surgical treatment or biopsy of the primary lesions and previous chemotherapy treatment consisting of MVAC. Previous chemotherapy with radiation therapy for local treatment in the primary lesion was allowed if it was completed at least 4 weeks before enrolment. Patients were eligible if their disease had progressed at any time after therapy to advanced or metastatic disease or within 12 months of neoadjuvant or adjuvant treatment. For inclusion in this study, patients were required to have an Eastern Cooperative Oncology Group performance status (PS) of two or lower per World Health Organization criteria; adequate bone marrow reserve [white blood cell (WBC) count higher than 3500/μl, platelet count higher than 100 000/μl and hemoglobin higher than 10 g/dl], hepatic function (serum bilirubin 1.5 mg/dl or less) and renal function (serum creatinine 1.5 mg/dl or measured creatinine clearance of at least 60 ml/min); and estimated life expectancy of at least 12 weeks. Patients with non-malignant systematic disease that precluded them from receiving therapy, including active infection, any clinically significant cardiac arrhythmia or congestive heart failure, were not eligible. Patients with central nerve system metastases, second primary malignant lesions or clinical significant pleural effusions or ascites or who had used any investigational agent 1 month before enrolment were not eligible. All patients gave written informed consent before entering this clinical trial. The study was approved by the institutional chemotherapy review board at Kitasato University Hospital and conducted in accordance with the Declaration of Helsinki.

Chemotherapy Regimen

We have previously shown the combined chemotherapy with GP (27). Briefly, all patients received paclitaxel 200 mg/m^2 on Day 1 and gemcitabine 1000 mg/m^2 on Days 1, 8 and 15. The treatment course was repeated every 3 weeks. On the first day of each course, full doses of both drugs were given if the WBC count was higher than 3000/μl and the platelet count was higher than 100 000/μl. If counts were lower than these levels, treatment was delayed for 1 week. On Days 8 and 15 of each cycle, full-dose gemcitabine was given if the patients had a WBC count higher than 3000/μl and a platelet count higher than 75 000/μl. Supportive care could include blood transfusion, antiemetics and analgesics. Prophylactic use of growth factors was not recommended. Further local therapy, including resection or radiation therapy, was allowed for patients with locally advanced disease after their responses to this regimen were assessed.

Treatment Evaluation

During treatment, blood counts and serum chemistries were carried out weekly, and creatinine clearance was calculated before chemotherapy. Tumors were assessed by computerized tomography or magnetic resonance imaging every two cycles, and responses were determined at least 4 weeks after administration.

Based on patient medical records, overall survival was measured until death and time to failure was measured until discontinuation of treatment, death or progression. Patients were assigned a response category according to the Response Evaluation Criteria in Solid Tumors guideline version 1.1 (28). Complete response (CR) was defined as the disappearance of all target lesions and reduction of any pathological lymph nodes (whether target or non-target) to <10 mm in the short axis. Partial response (PR) was defined as a decrease in the sum of diameters 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 had to also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions was also considered progression. Stable disease (SD) was defined as neither

sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Adverse events were monitored according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Patients who received at least one dose of GP were assessed for toxicity.

Statistical Analyses

For statistical analysis, PS (0 or 1 versus 2), age (<65 versus ≥65 years), visceral metastasis (negative versus positive), MVAC response (CR or PR versus SD or PD) and GP response (CR or PR versus SD or PD) were evaluated as dichotomized variables. Overall survival rate and response duration were calculated from the first day of GP treatment until the date of progression or death. Overall survival rate from previous chemotherapy was calculated from the first day of MVAC treatment until the date of death. Survival curves were analyzed with the Kaplan–Meier methods. Multivariate survival analyses were performed with the Cox proportional hazards regression model, controlling for PS, age, visceral metastasis, MVAC response and GP response. We developed a three-variable model of survival by added MVAC response based on the Bajorin prognostic risk factors (29). PS 0 or 1 was defined as 0 points and PS 2 was defined as 1 point. Negative visceral metastasis was defined as 0 points and positive was defined as 1 point. MVAC response (CR or PR) was defined as 0 points and MVAC response (SD or PD) was defined as 1 point. The patient group with low risk had 0 points, the intermediate risk group had 1 or 2 points and the high-risk group had 3 points. All analyses were performed with StatView, version 5.0 (SAS Institute, Cary, NC, USA), and $P < 0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

Between June 2005 and April 2010, 25 patients were treated with the GP regimen. One patient was excluded in this study because of not having received previous chemotherapy. The clinical characteristics of all patients are listed in Table 1. Of the 24 patients 21 were men and 3 were women, with a median age of 64.5 years (range, 48–79 years). Thirteen patients (54%) had bladder UC and 10 (42%) had upper urinary tract UC. All patients received one previous chemotherapy or chemoradiotherapy that consisted of MVAC treatment. Nine patients (38%) had lung metastases, 11 (46%) had lymph node metastases and 15 (63%) had one or more visceral metastases after MVAC chemotherapy.

Table 1. Patient characteristics

Characteristics	No. of patients
Sex	
Male/female	21/3
Age, years	
Median (range)	64.5 (48–79)
Performance status	
0/1/2	8/11/5
Primary organ	
Bladder/upper urinary tract	13/11
Surgical management	
Radical cystectomy	5
Partial cystectomy	1
Nephroureterectomy	8
TUR-BT	6
Lymphadectomy	2
Disease sites	
Lung	9
Lymph node	11
Liver	4
Bone	5
Primary site	7
Adrenal	1
Peritoneum	1
Prior treatment	
Chemotherapy	17
Chemoradiotherapy	7

TUR-BT, transurethral resection of the bladder tumor.

Treatment Received

Twenty-four eligible patients received at least two cycles of GP treatment and were evaluated for response. The median number of cycles was four (range, 1–12). The median dose intensity of paclitaxel and gemcitabine was 51.7 mg/m^2/week (range, 33.3–61.5 mg/m^2/week) and 775 mg/m^2/week (range, 500–923 mg/m^2/week), respectively. The median number of MVAC treatments before GP chemotherapy was four (range, 2–8). During treatment, a total of 86 cycles of GP chemotherapy were given. The percentages of the planned day 8 and 15 treatments actually given were 69 and 57%, respectively. Most of the omitted treatments were due to myelosuppression.

Treatment Efficacy

The objective tumor responses are shown in Table 2. Among the 24 patients, CR was confirmed in 2 patients (8%), and 8 patients (34%) showed PR, with an overall response rate of 42%. Disease control rate, which consisted of CR, PR and SD, was 71%. Among the 12 patients who received the GP treatment more than or equal to four cycles, 9 patients (75%)

Table 2. Response analysis of the 24 patients

Response	No. of patients	Response rate (%)
Complete response (CR)	2	8
Partial response (PR)	8	34
Stable disease (SD)	7	29
Progressive disease (PD)	7	29
Overall response rate (CR + PR)	10	42
Disease control rate (CR + PR + SD)	17	71

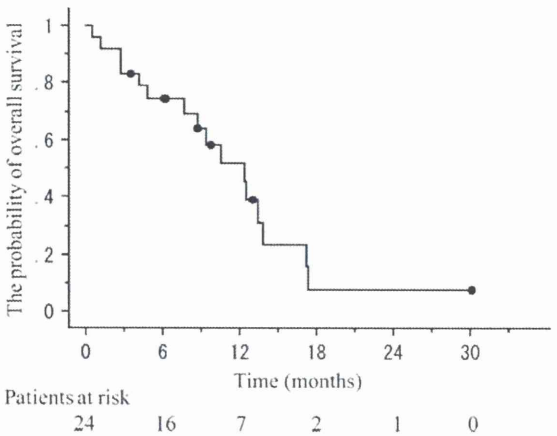

Figure 1. Overall survival curve ($n = 24$). The median survival time was 12.4 months, with 1-year and 2-year survival rates of 52 and 11%, respectively.

were good responders and 11 patients (92%) were good PS. However, in the 12 patients who received the GP treatment less than four cycles, PR was confirmed in only 1 patient (8%) and good PS was 8 patients (67%). After median follow-up of 20.4 months, 6 patients (25%) remain alive and 4 patients (17%) are progression-free. The overall median survival time was 12.4 months (range, 0.5–30.2 months). Survival rates were 52 and 11% in Years 1 and 2 of follow-up, respectively (Fig. 1). The median progression-free survival was 6.1 months (range, 0.5–23.9 months). The overall median survival time from MVAC chemotherapy was 20.3 months (range, 3.3–68.5 months).

According to multivariate Cox proportional hazards regression analysis, good PS and major response to MVAC treatment were significant predictors of overall survival and progression-free survival (Table 3). In addition, this model demonstrated differences in survival based upon the number of risk factors present in individual patients (Table 4). Patients with low risk (no risk factors) had a median survival time of 13.9 months and a 50% response rate. Patients with intermediate risk (one or two risk factors) had a median survival time of 12.4 months and a 43% response rate. For patients who had all risk factors, the median survival time was 2.7 months and response rate was 25%. There was a significant difference in survival profiles among the three risk groups ($P = 0.0072$).

Table 3. Multivariate Cox proportional hazards analysis of clinical findings for predicting clinical outcome following gemcitabine and paclitaxel (GP) treatment

Factors	Overall survival		Progression-free survival	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
PS	0.166	0.0344*	0.115	0.0061*
0.1 versus 2	(0.032–0.877)		(0.024–0.539)	
Age	1.577	0.4250	1.120	0.8245
<65 versus ≥65	(0.515–4.832)		(0.410–3.058)	
Visceral metastases	0.848	0.8224	1.463	0.6105
Negative versus positive	(0.201–3.574)		(0.339–6.320)	
MVAC response	0.178	0.0307*	0.149	0.0133*
CR + PR versus SD + PD	(0.037–0.851)		(0.033–0.673)	
GP response	1.239	0.7262	0.449	0.1879
CR + PR versus SD + PD	(0.374–4.108)		(0.136–1.480)	

PS, Eastern Cooperative Oncology Group performance status; MVAC, combined use of methotrexate, vinblastine, doxorubicin and cisplatin; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
*Significant at $P < 0.05$.

Table 4. Prognostic risk factors in a three-variable model

Prognostic group	*n*	ORR (%)	OS, months (range)	*P* value
Low (0)	6	3 (50%)	13.9 (3.5–17.3)	0.0072
Intermediate (1,2)	14	6 (43%)	12.4 (1.2–30.2)	
High (3)	4	1 (25%)	2.7 (0.5–10.6)	
Three-variable model				
Performance status	Visceral metastases		MVAC response	
0 = PS 0 or 1	0 = negative		0 = CR or PR	
1 = PS 2	1 = positive		1 = SD or PD	

ORR, overall response rate; OS, overall survival.

Table 5. Treatment-related toxicity

Adverse event	No. of patients			
	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	4	3	11	5
Thrombocytopenia	12	3	6	1
Febrile neutropenia	–	–	4	–
Neuropathy	1	7	–	–
Skin rash	–	3	–	–
Nausea/vomiting	3	1	–	–
Alopecia	7	–	–	–
Liver dysfunction	5	–	–	–

Adverse Events

The hematological and non-hematological toxicities in the 24 patients are listed in Table 5. Myelosuppression was the most common toxicity. Grade 3 neutropenia occurred in 11 patients (46%), and grade 4 occurred in 5 patients (21%). The patients were given granulocyte-colony stimulating factor (G-CSF) and responded to it very well. Febrile neutropenia was observed in four patients (17%); however, there were no severe infections. One patient (4%) experienced grade 4 thrombocytopenia, but did not report an episode of bleeding and platelet transfusions. Peripheral neuropathy was the most common non-hematologic toxicity. Eight patients (34%) experienced neuropathy and three patients (13%) experienced skin rash, but these were less than grade 3 toxicity. There were no treatment-related deaths in this study.

DISCUSSION

This study demonstrated that the GP regimen produces a 42% overall response rate and a 71% disease control rate with a tolerable toxicity profile as a second-line chemotherapy for advanced or metastatic UC patients who have previously been treated with MVAC chemotherapy. The median overall survival and progression-free survival were 12.4 and 6.1 months, respectively. In addition, 1-year survival was 52% after MVAC treatment failed. Although we have not formally collected the quality of life (QOL) data utilizing questionnaires, GP treatment supplied better QOL in most of the patients compared with MVAC treatment (91%, data not shown).

Many previous trials that assessed GP regimen have demonstrated a variable response rate of 30–69% (20–26). However, treatment strategies varied for the first-line or the second-line setting. For the second-line treatment, Suyama et al. (20) reported that the overall response rate was 33% and the disease control rate was 73%, with median overall survival of 11.3 months. Sternberg et al. (24) reported that overall response rate of an every 2 week regimen was 60%, and median overall survival was 14.4 months. Recently in a randomized phase III trial, Albers et al. (30) reported on the results of an every 3 weeks GP chemotherapy (short-term arm) versus an every 3 weeks GP chemotherapy until disease progression (prolonged arm). Overall survival was lower in both arms, with a median survival of 7.8 months for the short-term arm and 8.0 months for the prolonged arm. However, the overall response rate was 37.5 and 41.5%, respectively. These reports demonstrated therapeutic effects consistent with our results. How this regimen compares with other described regimens, including a variety of dose and treatment courses for patients with MVAC refractory cancer, is difficult to evaluate given the limited number of patients in this trial. Combined GP chemotherapy may possibly be useful for patients who were previously treated with cisplatin-based chemotherapy.

In several reports, the various prognostic factors of patients have been examined. Bajorin et al. (29) reported that a Karnofsky PS $<80\%$ and the presence of visceral (lung, liver or bone) metastases were independent prognostic factors for survival after first-line MVAC chemotherapy. Median survival times for patients who had zero, one or two risk factors were 33.0, 13.4 and 9.3 months, respectively. Bellmunt et al. (31) also reported that PS and visceral metastasis were important factors for patients who received the paclitaxel, cisplatin and gemcitabine regimen. Median survival times of patients with zero, one or two of these risk factors were 32.8, 18.0 and 10.6 months, respectively. Whether these two prognostic factors (PS and visceral metastasis) applied to our group of patients who had already received MVAC treatment is unclear. According to multivariate analysis in this study, good PS and major response to MVAC treatment were significant predictors of overall survival and progression-free survival. However, visceral metastasis was not a significant predictor for second-line treatment. Kanai et al. (32) reported that MVAC response was significantly associated with GP response. Therefore, we developed a three-variable model of survival by added MVAC response based on the Bajorin prognostic risk factors. Median survival times of patients treated with GP categorized in low, intermediate or high-risk groups were 13.9, 12.4 and 2.7 months, respectively. These three risk groups had a significant difference in survival profiles ($P = 0.0072$). The proportions of patients who obtained a major response to GP chemotherapy were 50%, 43 and 25% among patients with low risk, intermediate risk and high risk, respectively. These categorical variables may aid clinical decisions.

The clinical applicability of this regimen is supported by the outpatient administration and a tolerable toxicity profile in previously treated patients. Meluch et al. (25) reported that the severe adverse events following GP treatment included leukopenia (46%), anemia (28%) and thrombocytopenia (13%). Febrile neutropenia occurred in 10 patients (19%), and 1 patient (2%) had treatment-related death. In our study no life-threatening complications were seen. While

grade 3–4 neutropenia was frequently seen, these patients were safely treated using G-CSF and none had severe infections. Severe pulmonary toxicities such as interstitial pneumonitis were reported in another study (22). However, none of the 24 patients in our study experienced pulmonary toxicities, even though one patient received 12 cycles of GP treatment. Although it is not clear if pulmonary toxicities occur in a dose-dependent manner, these complications are more likely to occur with high-dose regimens (33).

Multidrug resistance (MDR) of tumors is frequently associated with decreased cellular accumulation of anticancer drugs. Therefore, it is of importance to investigate the correlation between MDR gene expression and cisplatin resistance (34). Hoffmann et al. (35) reported that high *MDR1* and excision repair cross-complementing 1 (*ERCC1*) gene expression was associated with inferior outcome after cisplatin-based chemotherapy for locally advanced bladder cancer. According to this mechanism, a MVAC non-responder would show resistance to the GP chemotherapy. As new drugs such as GP have been introduced to the management of urothelial cancer, biomarkers including *MDR1* and *ERCC1* would be required to select appropriate treatment options for individualized patient care.

GP treatment was effective for advanced or metastatic UC previously treated with MVAC. In addition to MVAC, GC treatment is currently a favorable and a less toxic regimen as first-line chemotherapy. In several reports, the second-line chemotherapy regimen is reported after GC failure. Albers et al. (30) reported that second-line GP treatment demonstrated ~40% response rate. Kitamura et al. (36) reported that second-line paclitaxel, ifosfamide and nedaplatin treatment demonstrated 40% overall response rate, 8.9 months overall survival and 4.0 months progression-free survival. In the GC era, it is difficult for us to choose the treatment drug as second-line chemotherapy. However, we think that the previous cisplatin-based chemotherapy may have interaction with the effect of the GP regimen as second-line treatment.

Limitations of this study are that efficacy and tolerability data for GP treatment in a second-line setting were evaluated retrospectively and not in a randomized trial. Additional limitations include the small sample size and relatively short follow-up. Although our analysis relied on a small sample size, 10 patients (42%) who were treated with the GP regimen had major response and disease control was confirmed in 17 patients (71%). GP chemotherapy itself did not have prognostic effects in multivariate analyses, however, it may have interaction with MVAC, in which case it may lead to having clinically additive effects and to improving the prognosis as a second-line treatment. We will investigate much more number of cases in the future, and will examine whether the GP treatment would give merely improved QOL or become the factor that would affect overall survival and progression-free survival. However, this regimen is effective and safe as a second-line treatment for patients with advanced or metastatic UC.

CONCLUSIONS

GP chemotherapy as a second-line treatment is a favorable and alternative regimen for advanced or metastatic UC previously treated with MVAC. Given the safety and benefit profile seen in this trial, two important factors—good PS and major response of MVAC treatment—were significant predictors of overall survival and progression-free survival. The GP regimen is recommended as a potentially favorable modality for second-line chemotherapy for advanced or metastatic UC.

Conflict of interest statement

None declared.

References

1. Sternberg CN, Yagoda A, Scher HI, Watson RC, Ahmed T, Weiselberg LR, et al. Preliminary results of M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for transitional cell carcinoma of the urothelium. *J Urol* 1985;133:403–7.
2. Loehrer PJ, Sr, Einhorn LH, Elson PJ, Crawford ED, Kuebler P, Tannock I, 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;10:1066–73.
3. Sternberg CN, Yagoda A, Scher HI, Watson RC, Geller N, Herr HW, et al. Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. *Cancer* 1989;64:2448–58.
4. Sternberg CN, Yagoda A, Scher HI, Watson RC, Herr HW, Morse MJ, et al. M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for advanced transitional cell carcinoma of the urothelium. *J Urol* 1988;139:461–9.
5. Saxman SB, Propert KJ, Einhorn LH, Crawford ED, Tannock I, Raghavan D, et al. Long-term follow-up of a phase III intergroup study of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. *J Clin Oncol* 1997;15:2564–9.
6. von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, et al. 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;23:4602–8.
7. von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, et al. 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;18:3068–77.
8. Soga N, Onishi T, Arima K, Sugimura Y. Paclitaxel carboplatin chemotherapy as a second-line chemotherapy for advanced platinum resistant urothelial cancer in Japanese cases. *Int J Urol* 2007;14:828–32.
9. Kouno T, Ando M, Yonemori K, Matsumoto K, Shimizu C, Katsumata N, et al. Weekly paclitaxel and carboplatin against advanced transitional cell cancer after failure of a platinum-based regimen. *Eur Urol* 2007;52:1115–22.
10. Vaishampayan UN, Faulkner JR, Small EJ, Redman BG, Keiser WL, Petrylak DP, et al. Phase II trial of carboplatin and paclitaxel in cisplatin-pretreated advanced transitional cell carcinoma: a Southwest Oncology Group study. *Cancer* 2005;104:1627–32.
11. Lin CC, Hsu CH, Huang CY, Keng HY, Tsai YC, Huang KH, et al. Gemcitabine and ifosfamide as a second-line treatment for cisplatin-refractory metastatic urothelial carcinoma: a phase II study. *Anticancer Drugs* 2007;18:487–91.
12. Pectasides D, Aravantinos G, Kalofonos H, Kiamouris C, Bafaloukos D, Xiros N, et al. Combination chemotherapy with gemcitabine and ifosfamide as second-line treatment in metastatic urothelial cancer. A

phase II trial conducted by the Hellenic Cooperative Oncology Group. *Ann Oncol* 2001;12:1417–22.
13. Dreicer R, Manola J, Schneider DJ, Schwerkoske JF, George CS, Roth BJ, et al. Phase II trial of gemcitabine and docetaxel in patients with advanced carcinoma of the urothelium: a trial of the Eastern Cooperative Oncology Group. *Cancer* 2003;97:2743–7.
14. Pagliaro LC, Millikan RE, Tu SM, Williams D, Daliani D, Papandreou CN, et al. Cisplatin, gemcitabine, and ifosfamide as weekly therapy: a feasibility and phase II study of salvage treatment for advanced transitional-cell carcinoma. *J Clin Oncol* 2002;20:2965–70.
15. Krege S, Rembrink V, Borgermann C, Otto T, Rubben H. Docetaxel and ifosfamide as second line treatment for patients with advanced or metastatic urothelial cancer after failure of platinum chemotherapy: a phase 2 study. *J Urol* 2001;165:67–71.
16. Roth BJ, Dreicer R, Einhorn LH, Neuberg D, Johnson DH, Smith JL, et al. Significant activity of paclitaxel in advanced transitional-cell carcinoma of the urothelium: a phase II trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 1994;12:2264–70.
17. Sternberg CN. Gemcitabine in bladder cancer. *Semin Oncol* 2000;27:31–9.
18. Stadler WM, Kuzel T, Roth B, Raghavan D, Dorr FA. Phase II study of single-agent gemcitabine in previously untreated patients with metastatic urothelial cancer. *J Clin Oncol* 1997;15:3394–8.
19. Shord SS, Faucette SR, Gillenwater HH, Pescatore SL, Hawke RL, Socinski MA, et al. Gemcitabine pharmacokinetics and interaction with paclitaxel in patients with advanced non-small-cell lung cancer. *Cancer Chemother Pharmacol* 2003;51:328–36.
20. Suyama T, Ueda T, Fukasawa S, Imamura Y, Nakamura K, Miyasaka K, et al. Combination of gemcitabine and paclitaxel as second-line chemotherapy for advanced urothelial carcinoma. *Jpn J Clin Oncol* 2009;39:244–50.
21. Fechner G, Siener R, Reimann M, Kobalz L, 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.
22. Li J, Juliar B, Yiannoutsos C, Ansari R, Fox E, Fisch MJ, et al. Weekly paclitaxel and gemcitabine in advanced transitional-cell carcinoma of the urothelium: a phase II Hoosier Oncology Group study. *J Clin Oncol* 2005;23:1185–91.
23. Kaufman DS, Carducci MA, Kuzel TM, Todd MB, Oh WK, Smith MR, et al. A multi-institutional phase II trial of gemcitabine plus paclitaxel in patients with locally advanced or metastatic urothelial cancer. *Urol Oncol* 2004;22:393–7.
24. Sternberg CN, Calabro F, Pizzocaro G, Marini L, Schnetzer S, 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;92:2993–8.
25. Meluch AA, Greco FA, Burris HA, III, O'Rourke T, Ortega G, Steis RG, et al. 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: 3018–24.
26. Takahashi T, Higashi S, Nishiyama H, Segawa T, Nakamura E, Kinoshita H, et al. Biweekly paclitaxel and gemcitabine for patients with advanced urothelial cancer ineligible for cisplatin-based regimen. *Jpn J Clin Oncol* 2006;36:104–8.
27. Matsumoto K, Irie A, Satoh T, Okazaki M, Iwamura M, Baba S. Gemcitabine and paclitaxel chemotherapy as a second-line treatment for advanced or metastatic urothelial carcinoma. *Int J Urol* 2007;14:1000–4; discussion 4.
28. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.
29. Bajorin DF, Dodd PM, Mazumdar M, Fazzari M, McCaffrey JA, Scher HI, et al. Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. *J Clin Oncol* 1999;17:3173–81.
30. Albers P, Park SI, Niegisch G, Fechner G, Steiner U, Lehmann J, et al. Randomized phase III trial of 2nd line gemcitabine and paclitaxel chemotherapy in patients with advanced bladder cancer: short-term versus prolonged treatment [German Association of Urological Oncology (AUO) trial AB 20/99]. *Ann Oncol* 2011;22:288–94.
31. Bellmunt J, Albanell J, Paz-Ares L, Climent MA, Gonzalez-Larriba JL, Carles J, et al. Pretreatment prognostic factors for survival in patients with advanced urothelial tumors treated in a phase I/II trial with paclitaxel, cisplatin, and gemcitabine. *Cancer* 2002;95:751–7.
32. Kanai K, Kikuchi E, Ohigashi T, Miyajima A, Nakagawa K, Nakashima J, et al. Gemcitabine and paclitaxel chemotherapy for advanced urothelial carcinoma in patients who have received prior cisplatin-based chemotherapy. *Int J Clin Oncol* 2008;13:510–4.
33. Dunsford ML, Mead GM, Bateman AC, Cook T, Tung K. Severe pulmonary toxicity in patients treated with a combination of docetaxel and gemcitabine for metastatic transitional cell carcinoma. *Ann Oncol* 1999;10:943–7.
34. Choi MK, Kim DD. Platinum transporters and drug resistance. *Arch Pharm Res* 2006;29:1067–73.
35. Hoffmann AC, Wild P, Leicht C, Bertz S, Danenberg KD, Danenberg PV, et al. MDR1 and ERCC1 expression predict outcome of patients with locally advanced bladder cancer receiving adjuvant chemotherapy. *Neoplasia* 2010;12:628–36.
36. Kitamura H, Taguchi K, Kunishima Y, Yanase M, Takahashi A, Shigyo M, et al. Paclitaxel, ifosfamide, and nedaplatin as second-line treatment for patients with metastatic urothelial carcinoma: a phase II study of the SUOC group. *Cancer Sci* 2011;102:1171–5.

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UROLOGY – REVIEW

Current chemotherapeutic strategies against bladder cancer

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Abstract Urothelial cancer is a chemotherapy-sensitive malignancy, with the regimen of methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) until recently considered to be the first choice for chemotherapy. Poor survival and substantial toxicity associated with M-VAC have led to investigations into alternative chemotherapy strategies, and the combination of gemcitabine and cisplatin (GC) may be promising. In addition, combination chemotherapy of taxanes along with gemcitabine and/or platinum-based agents is also considered to provide clinical benefits as second-line chemotherapy following M-VAC or GC therapy. In the near future, results of trials using molecular target therapies may bring improved outcomes for patients with bladder cancer.

Keywords Bladder cancer · Chemotherapy · Urothelial cancer

Introduction

Most cases of urothelial cancer show high sensitivity to chemotherapeutic agents. Steinberg et al. reported that the first choice of chemotherapy for patients with metastatic or unresectable bladder cancer was the four-drug regimen of methotrexate, vinblastine, doxorubicin, and cisplatin (CDDP) (M-VAC) therapy, and this regimen was until recently considered to be the gold standard [1, 2]. However, M-VAC therapy to improve the prognosis of urothelial cancer has not shown to be as effective as hoped, with less than 5% of affected patients reported to have long-term disease-free survival. In addition, chemotherapy for patients showing M-VAC resistance or recurrent cases after first-line chemotherapy remains to be unestablished. In order to overcome the disadvantages of M-VAC chemotherapy, several trials utilizing new chemotherapeutic agents, such as taxanes (paclitaxel: PTX, docetaxel: DOC) and gemcitabine (GEM), are ongoing. In addition, development of several potential molecular target therapies would surely provide new insight into improving the prognosis of bladder cancer patients. In this review, we discuss the present status of bladder cancer chemotherapy and applications to improve the prognosis of bladder cancer patients.

Neoadjuvant approach

Locally advanced bladder cancer undergoing radical cystectomy shows a high recurrence rate after radical surgery. However, preoperative chemotherapy can improve its prognosis. Indeed, neoadjuvant chemotherapy has several advantages, including (1) accurate evaluation of the prognosis of each individual patient

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based on in vivo sensitivity analysis of chemotherapeutic agents, (2) possible down-staging (if effective), contributing easy manipulation during radical surgery, (3) inhibitory effect on possible micrometastasis, (4) full-dosage application of chemotherapeutic agents due to preoperative better performance status (PS), and (5) possible preservation of the original bladder. Conversely, disadvantages of neoadjuvant chemotherapy are known as follows: (1) delayed radical surgery, owing to the time used for chemotherapy and (2) no pathological information regarding bladder cancer or inadequate pathological staging leading to possible overtreatment.

Presently, conventional neoadjuvant chemotherapy should include platinum-based compounds. The clinical benefits of neoadjuvant chemotherapy with platinum-based compounds were evaluated in a study that employed meta-analysis, which included 2688 cases with T2-T4a disease, and showed that neoadjuvant chemotherapy allowed 5–6.5% more bladder cancer patients to survive at 5 years after radical surgery [3]. In this study, the pT0 rate, indicating complete pathological remission, was between 30% and 40%, which appears to be somewhat higher than expected based on the 5-year survival rate, suggesting some doubtful beneficial effects of neoadjuvant chemotherapy toward micrometastasis already present at an early stage. Another meta-analysis of 3005 cases published in 2005 found that neoadjuvant chemotherapy using platinum-based compounds improved the survival of patients with locally advanced bladder cancer [4]. In the future, a randomized controlled trial (RCT) using newly developed chemotherapeutic agents might be necessary to establish a safer and more effective neoadjuvant chemotherapy strategy.

Adjuvant approach

Chemotherapy following radical surgery (adjuvant chemotherapy) provides several advantages, such as (1) no delay in undergoing a radical operation, (2) significant mass reduction prior to chemotherapy, and (3) a clarified requirement for chemotherapy after radical surgery based on accurate pathological information from surgical specimens. However, the major drawback of adjuvant chemotherapy is that the original bladder cannot be preserved. Several RCTs of adjuvant chemotherapy, including cases with pT3-T4N0 or N1 disease, have shown the limited value of an adjuvant approach, namely improvement of time-to-progression (TTP) to some extent, but no significant effect on longer survival [5–9]. A meta-analysis of adjuvant chemotherapy published in 2005 of 491 cases found that the risk of death in the adjuvant arm was reduced to 25% [10]. In order to provide definitive evidence of the effects of adjuvant chemotherapy in light of survival benefit, future analyses should also focus on the rationale of the selection and timing of chemotherapeutic agents in a large number of cases. Recent randomized phase III trial of combination chemotherapy with PTX, GEM, and CDDP (PGC) reported at ASCO congress 2010 by the Spanish Oncology Genitourinary Group Study (SOGUG) 99/01 has shown that adjuvant setting of PGC combination significantly improved not only disease-free survival but also overall survival (OS) after radical cystectomy in patients with high-risk, invasive bladder cancer [11]. This promising outcome of adjuvant PGC chemotherapy could help establish an effective postoperative chemotherapeutic strategy against invasive bladder cancer in the upcoming future.

Chemotherapy for unresectable or metastatic disease

(a) M-VAC and modifications

Combination chemotherapy should contribute to survival benefit and it is now accepted that the use of M-VAC therapy [1, 2] with cisplatin, methotrexate, and vinblastine (CMV) [12] can improve the response rate (RR) in patients with unresectable or metastatic disease. An early result of M-VAC therapy showed an RR of more than 50% and improved survival rate of 3 years for between 20 and 25% of the analyzed patients, with a median survival period of 13 months [1]. Although a survival benefit with M-VAC therapy as compared to the combination chemotherapy of CDDP, cyclophosphamide, and adriamycin (CISCA) has been shown, the major concern is the higher incidence of adverse effects of mucositis in addition to myelosuppression in the M-VAC arm [13]. Considering that the majority of patients with advanced bladder

cancer are elderly and more likely to have potential complications, chemotherapy often cannot be performed without reducing the dosage or changing the chemotherapeutic agents, which may decrease the chemotherapeutic benefit. Maintaining dose intensity is mandatory to achieve a stable effect of chemotherapeutic agents on bladder cancer. On the other hand, high-dose M-VAC (HD-M-VAC) with granulocyte colony-stimulating factor (G-CSF) is beginning to be recognized as a superior and tolerable therapy. The RR of HD-M-VAC with G-CSF was significantly higher than that of standard M-VAC (58% vs. 72%) [14]. Furthermore, prognostic analysis of that phase III trial conducted in 2001 showed that the progression-free survival (PFS) with HD-M-VAC was significantly superior to that with standard M-VAC, whereas there was no significant difference in OS found between the 2 modalities [14]. A more recent analysis conducted in 2006 also clearly demonstrated significant improvement of OS in addition to PFS after 5 years with HD-M-VAC as compared to standard M-VAC, as the OS values at 5 years were 21.8 and 13.5%, respectively [15]. In addition, the incidence of myelosuppression, such as neutropenia and thrombocytopenia, was lower in the HD-M-VAC arm [16]. Thus, addition of G-CSF to HD-M-VAC could become a novel modality for bladder cancer chemotherapy (Fig. 1).

(b) Combination with platinum-based compounds (2 drugs combined)

The anticancer activity of taxanes is accelerated when combined with CDDP. The Eastern Cooperative Oncology Group Study (ECOG) phase II trial of combination chemotherapy with PTX and CDDP showed an overall RR of 50% (complete response rate of 7.7%) with a median survival of 10.6 months, while mild reverse effects of granulocytopenia and neurotoxicity appeared to be common [15]. Another phase II trial of combination chemotherapy of DOC with CDDP (DC) showed that the overall RR of 50–60% was nearly identical to that of PC, while the incidence of neurotoxicity and fluid storage was lower in DC compared with PC [17, 18]. In an RCT that compared M-VAC (109 cases) under G-CSF administration with DC (111 cases), the M-VAC arm showed superior efficacy for both overall RR and TTP, though the incidence of neutropenia, thrombocytopenia, and neutropenia-related septicemia was significantly higher with the former protocol [19]. Thus, at the present time, considering the potential balance between efficacy and tolerance, the priority of combination chemotherapy of taxanes with CDDP over M-VAC remains not to be determined.

GEM is an anticancer drug that is metabolized in the liver, and additional cytotoxic effects can be enhanced when administered with CDDP [20]. In an RCT that compared between the combinations of GEM with CDDP (GC) and M-VAC, no significant differences in overall RR, TTP, and OS were found between the two arms, while the rates of incidence of myelosuppression, oral mucosal impairment, body weight loss, and general fatigue were significantly lower with GC as compared to M-VAC. Furthermore, the dose intensity of the GC arm was significantly superior to that of the M-VAC arm. Recent results

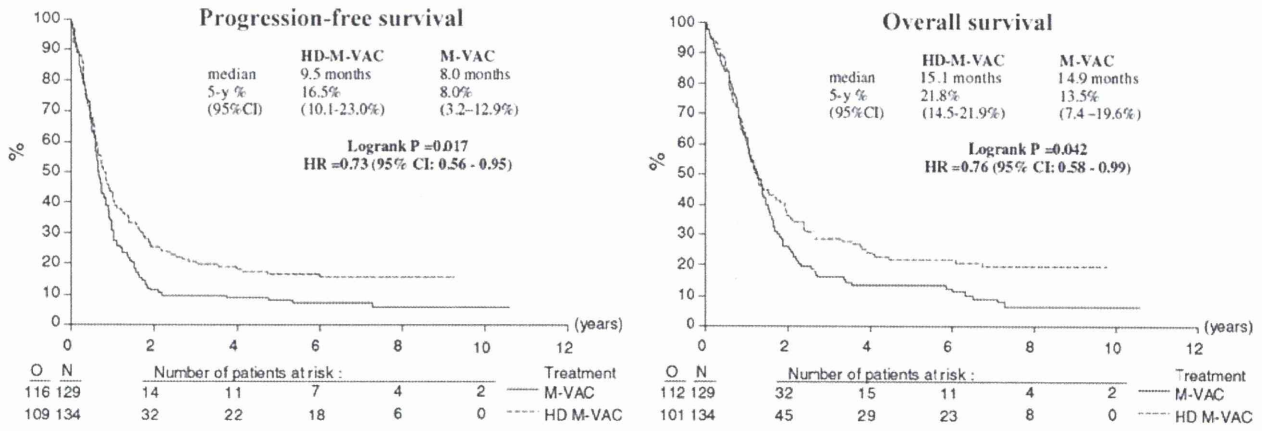

Fig. 1 High-dose M-VAC versus classic M-VAC

with a longer follow-up period demonstrated no difference in 5-year survival (GC: 13%; M-VAC: 15.3%) and PFS (GC: 9.8%; M-VAC: 11.3%) (Fig. 2) [21].Considering better tolerance and QOL related to GC, this combination therapy is a promising chemotherapeutic regimen for advanced urothelial cancer [22].

There were several trials substituted CDDP with carboplatin (CBDCA) in attempts to diminish the potential nephrotoxicity of the anticancer drugs. In phase II trials of the combination of PTX with CBDCA (CP), the overall RR ranged from 14 to 65%, which was probably because of the different dosages used in each trial (PTX: 150–225 mg/mm; CBDCA: AUC 5-6) [23–26]. An RCT of ECOG in comparison to CP with M-VAC (median follow-up: 32.5 months) showed no significant differences in overall RR (CP 28.2%, M-VAC 35.9%), PFS (median) (CP: 5.2 months; M-VAC: 8.7 months), or overall survival (median) (CP: 13.8 months, M-VAC: 15.4 months) [27]. However, this trial was too small with a short follow-up period, and accumulation of longer-term follow-up data should be needed to identify whether CP or M-VAC has a greater survival benefit.

(c) Combination with platinum-based compounds (3 drugs combined)

In a phase I/II trial of a GCP regimen (GEM + CDDP + PTX), a high overall RR of 77.6% (CR 27.6% and PR 50%) was obtained [28]. Even when the analysis was limited to metastatic cases, the overall RR was 66.6%. Adverse effects included grade 3/4 neutropenia (55%) and thrombocytopenia (22%), though only 4% of the cases experienced peripheral nerve impairment [28]. In a phase II trial that compared GCP (GEM + CDDP + PTX) with GC (GEM + CDDP) with 85 cases, no significant

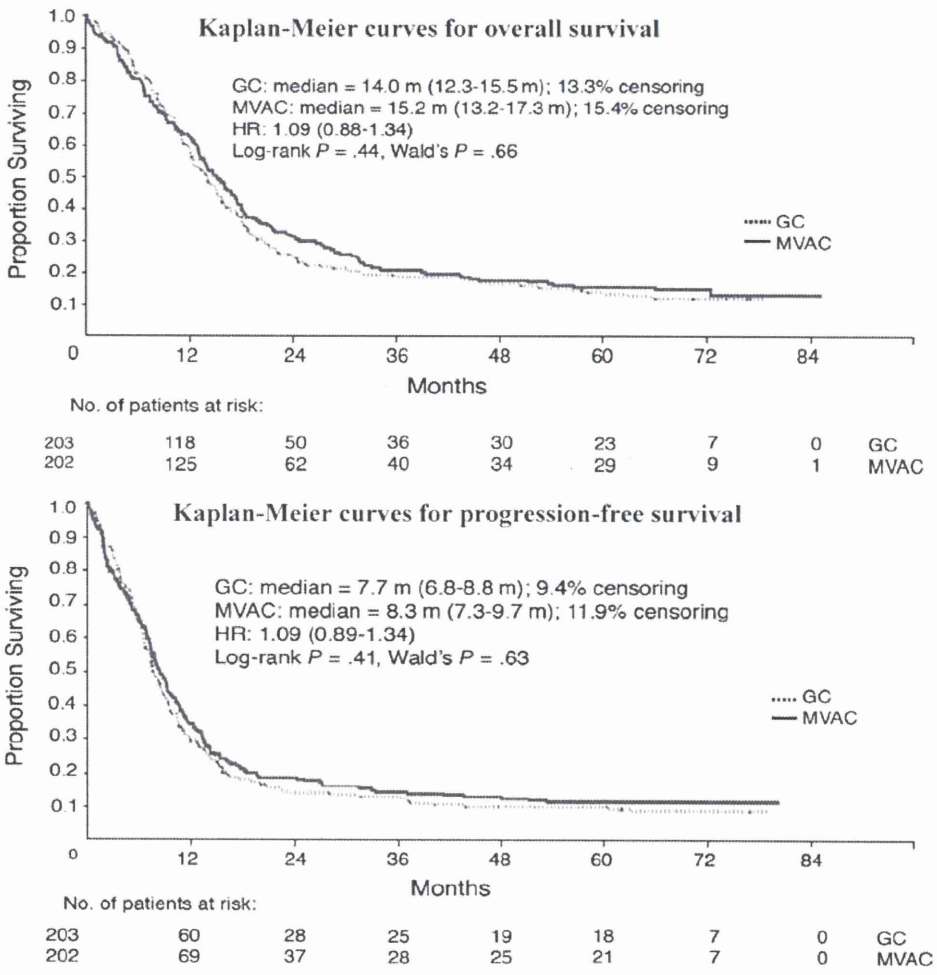

Fig. 2 GC therapy versus M-VAC therapy

differences in overall RR (GCP: 43% and GC: 44%) or overall survival (GCP: 61 weeks and GC: 49 weeks) were found between the two regimens [29]. Another phase III trial of EORTC-30987 employing 626 cases is ongoing and is intended to examine the difference in survival benefit between GCP and GC. A phase II trial of the combined therapy of GEM, CDDP, and DOC instead of PTX clearly showed the clinical benefit of this regimen with a high overall RR (CR: 28.5%, PR: 37.1%), indicating that GEM + CDDP + DOC is a promising combination chemotherapy with tolerable adverse effects of grade 3/4 neutrocytopenia, anemia, and thrombocytopenia occurring in 20 to 30% of the patients [30].

ITP therapy comprising of ifosfamide (IFM), CDDP, and PTX was first applied in the Memorial Sloan-Kettering Cancer Center for 29 bladder cancer cases, which resulted in an excellent overall RR (CR in six cases, PR in 17 cases) [31]. Although adverse effects such as hair loss, allergic reactions, renal impairment, and peripheral nerve disturbance in addition to myelosuppression were found in that series, survival analysis demonstrated the longest survival time (median: 20 months) among conventional chemotherapy regimens. At present, no RCT has compared the survival benefits between ITP and M-VAC.

(d) Combination without platinum-based compounds

Much novel chemotherapy of taxanes with GEM or IFM has been developed to avoid the significant adverse effects caused by CDDP without decreasing the survival benefit of the drug combination. In a phase II trial of GEM at 1,000 mg/m^2 combined with PTX at 110 mg/m^2 (days 1, 8, and 15), repeated every 28 days, an excellent overall RR (69.4%) was found along with frequent lung toxicity (pulmonary fibrosis), as well as myelosuppression and nerve disturbance [32]. In contrast, in a phase II trial of the combination of GEM at 1,000 mg/m^2 (days 1 and 8) and DOC at 75 mg/m^2 (day 8), repeated every 21 days, the overall RR of 51.6% was higher in spite of the substitution of PTX with DOC. Despite the finding that about 40% of cases have a past history of impaired cardiac function, chemotherapy-related death was not encountered and there was a minimal incidence of grade 3/4 adverse effects, including anemia (6.7%), thrombocytopenia (4.9%), and neutrocytopenia (27.6%), indicating that the combination of GEM and DOC can be safely applied for patients with impaired kidney and heart functions [33]. The overall RR in the phase II trial of IFM monotherapy was around 20% [34], while that in patients who received the combination of IFM (1000 mg/m^2) and PTX (135 mg/m^2) reached 30.7% in first-line cases and 15.4% in second-line cases with history of a CDDP-based regimen [35]. In addition, the only adverse side-effect was grade 3/4 myelosuppression, and significant septicemia was not encountered. Thus, this combination approach using IFM and PTX may be suitable for second-line chemotherapeutic regimen.

Second-line chemotherapy

Appropriate chemotherapy for CDDP-resistant or CDDP-recurrent cases has not been established. Notably, recurrent cases after first-line chemotherapy frequently show myelofunctional impairment, in addition to worsened PS and/or impaired renal function, thus second-line chemotherapy is often difficult. The combination regimen of taxanes with GEM appears to provide clinical benefits following standard M-VAC therapy [36]. However, definite evidence was not shown in those trial results due to insufficient analysis, as the study did not focus on only recurrent and/or refractory cases after first-line chemotherapy. In general, taxanes are often used in second-line therapy cases, in which the overall RRs of DOC and PTX have been reported to be 13% [37] and 42–56% [38, 39], respectively. The overall RR of GEM monotherapy was around 25% irrespective of a previous history of chemotherapy, suggesting that GEM exerts an anticancer effect on CDDP-resistant cases [40, 41]. In a phase II trial of the combination of PTX (150 mg/m^2) and GEM (2500–3,000 mg/m^2) given every 2 weeks to 41 patients who had previously received CDDP-based chemotherapy, excellent overall RR (60%) and survival period (median: 14.4 months) were confirmed [42]. Likewise, the overall RR of PTX + GEM as induction therapy (including several newly diagnosed cases) was reported to be 54% [36]. A pilot study of the combination chemotherapy using GEM, DOC, and CBDCA (GDC) also showed the beneficial effect on the patients having had the resistance against CDDP-based chemotherapy, in which despite 8 cases having had GC resistance, 6 of 9 cases (67%) archived