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

Masaomi Ikeda*, Kazunasa Matsumoto, Ken-ichi Tabata, Satoru Minamida, Tetsuo Fujita, Takefumi Satoh, Masatsugu Iwamura and Shiro Baba

Department of Urology, Kitasato University School of Medicine, Kanagawa, Japan

*For reprints and all correspondence: Masaomi Ikeda, Department of Urology, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0374, Japan. E-mail: ikeda.masaomi@grape.plala.or.jp

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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/m² on Day 1 and gemcitabine 1000 mg/m² on Days 1, 8 and 15. The gemcitabine and paclitaxel regimen was repeated every 3 weeks.

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.

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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 chemotherapy 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 (27). 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 systemic 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/m² on Day 1 and gemcitabine 1000 mg/m² 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 StafView, 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.

**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/m²/week (range, 33.3–61.5 mg/m²/week) and 775 mg/m²/week (range, 500–923 mg/m²/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%)
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 2. Response analysis of the 24 patients

<table>
<thead>
<tr>
<th>Response</th>
<th>No. of patients</th>
<th>Response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>8</td>
<td>34</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>7</td>
<td>29</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>7</td>
<td>29</td>
</tr>
<tr>
<td>Overall response rate (CR + PD)</td>
<td>10</td>
<td>42</td>
</tr>
<tr>
<td>Disease control rate (CR + PR + SD)</td>
<td>17</td>
<td>71</td>
</tr>
</tbody>
</table>

**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.

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

<table>
<thead>
<tr>
<th>Factors</th>
<th>Overall survival</th>
<th>Progression-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>$P$ value</td>
</tr>
<tr>
<td>PS</td>
<td>0.166</td>
<td>0.0344*</td>
</tr>
<tr>
<td>0.1 versus 2 (0.032–0.877)</td>
<td>(0.024–0.539)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.577</td>
<td>0.4250</td>
</tr>
<tr>
<td>&lt;65 versus $\geq$ 65</td>
<td>(0.515–4.832)</td>
<td>(0.410–3.058)</td>
</tr>
<tr>
<td>Visceral metastases</td>
<td>0.848</td>
<td>0.8224</td>
</tr>
<tr>
<td>Negative versus positive</td>
<td>(0.201–3.574)</td>
<td>(0.339–6.320)</td>
</tr>
<tr>
<td>MVAC response</td>
<td>0.178</td>
<td>0.0307*</td>
</tr>
<tr>
<td>CR + PR versus SD + PD</td>
<td>(0.037–0.851)</td>
<td>(0.033–0.673)</td>
</tr>
<tr>
<td>GP response</td>
<td>1.239</td>
<td>0.7262</td>
</tr>
<tr>
<td>CR + PR versus SD + PD</td>
<td>(0.374–4.108)</td>
<td>(0.136–1.480)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Prognostic group</th>
<th>$n$</th>
<th>ORR (%)</th>
<th>OS, months (range)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (0)</td>
<td>6</td>
<td>3 (50%)</td>
<td>13.9 (3.5–17.3)</td>
<td>0.0072</td>
</tr>
<tr>
<td>Intermediate (1,2)</td>
<td>14</td>
<td>6 (43%)</td>
<td>12.4 (12.1–30.2)</td>
<td></td>
</tr>
<tr>
<td>High (3)</td>
<td>4</td>
<td>1 (25%)</td>
<td>2.7 (0.5–10.6)</td>
<td></td>
</tr>
</tbody>
</table>

Performance status, Visceral metastases, MVAC response

ORR, overall response rate; OS, overall survival.
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 4 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

<table>
<thead>
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<th>Table 5. Treatment-related toxicity</th>
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<tr>
<td>Adverse event</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td>Neuropathy</td>
</tr>
<tr>
<td>Skin rash</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
</tr>
<tr>
<td>Alopecia</td>
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<tr>
<td>Liver dysfunction</td>
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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 antican-cer 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


