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ORIGINAL ARTICLE

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# Salvage chemotherapy with paclitaxel, ifosfamide, and nedaplatin in patients with urothelial cancer who had received prior cisplatin-based therapy

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**Abstract** *Background and aims:* The aim of the present phase II study was to evaluate the efficacy of combination chemotherapy of paclitaxel, ifosfamide, and nedaplatin (PIN regimen) in patients with recurrent urothelial cancer who had been treated with cisplatin-based chemotherapy. *Patients/methods:* Eligible patients were those with histologically confirmed urothelial cancer who had progressed or relapsed after cisplatin-based chemotherapy. The PIN regimen consisted of paclitaxel 175 mg/m$^2$ on day 1; ifosfamide 4.5 g/m2 divided over days 1, 2, and 3; and nedaplatin 70 mg/m$^2$ on day 1; PIN was given every 28 days. *Results:* Among the 32 patients enrolled in the study (median age, 66 years), complete and partial responses were obtained in 5 patients and 19 patients, respectively, with an overall response rate of 75% (95% confidence interval [CI], 59–91%). The median time to progression was 8 months (range, 0–50+ months) and the median survival was 22 months (range, 4–52+ months). The 1- and 2-year overall survival rates were 53.7 and 42.9%, respectively. All patients experienced Grade 3 or 4 neutropenia, while Grade 3 or 4 thrombocytopenia was seen in 8 patients; Grade 3 or 4 anemia was seen in 6 patients; Grade 3 neuropathy was observed in 1 patient, for whom the PIN therapy was discontinued. There were no treatment-related deaths. *Conclusion:* The PIN combination was highly active and tolerable in previously treated patients with urothelial cancer as a second-line treatment.

**Keywords** Salvage chemotherapy · Paclitaxel · Ifosfamide · Nedaplatin · Urothelial cancer

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## Introduction

Systemic chemotherapy is the only current treatment modality for metastatic and unresectable urothelial cancer. Prior to the development of effective chemotherapy the median survival of patients with metastatic urothelial cancer rarely exceeded 6 months. Since the report by Sternberg et al. [1], the situation has dynamically changed. Modern cisplatin-based combination chemotherapy regimens have shown overall response proportions of approximately 40–70% [1, 2]. Of these, the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) has become the standard treatment [3–6]. On the other hand, a prospective randomized trial conducted in Japan showed that the

response rate and the incidence of adverse effects for the combination of methotrexate, epirubicin, and cisplatin (MEC) was almost equal to that for M-VAC [7]. MEC combination for patients with metastatic urothelial cancer is relatively popular in Japan. Although M-VAC and MEC are highly effective, the majority of responders unfortunately relapse and die as a result of recurrent disease. Thus, the development of an innovative treatment option is clearly needed.

In such circumstances, several phase II trials have been performed for patients who have been previously treated with chemotherapy. However, potent salvage chemotherapy for these patients does not yet exist [8]. To establish a novel-treatment approach, one of the currently available therapeutic options might be to use innovative chemotherapeutic agents. New active agents have been identified as being effective in patients with bladder cancer. Of these, paclitaxel has produced a 42% response rate, with 27% achieving a CR, in patients who have not had prior therapy [9]. The promising results of first-line single-agent treatment with paclitaxel have prompted the use of paclitaxel-based combination chemotherapy against advanced urothelial cancer. Of these, the combination of paclitaxel, cisplatin, and ifosfamide (ITP) is one of the most practically implemented regimens against chemo-naïve advanced urothelial cancer [10]. When we considered the development of salvage chemotherapy for patients with urothelial cancer who had received prior cisplatin-based chemotherapy, we took note of the favorable results of the ITP regimen and supposed that some modifications from the original ITP regimen might be required because of anticancer activity and the patient's status, which were disordered by prior chemotherapy. For these reasons, cisplatin in the original ITP regimen was replaced by nedaplatin. Nedaplatin (cis-diammine-glycolate-0,0' platinum II, CDGP) is a new cisplatin analog that has shown equivalent antitumor activity and lower toxicity-less nausea, and lower nephrotoxicity and neurotoxicity than cisplatin, although its hematological toxicity can be a limiting factor at high dosage, as found with Carboplatin [11, 12]. In the phase II study, nedaplatin monotherapy generated a 28% response rate against bladder cancer [13], which was similar to the response rate of cisplatin and was higher than the 15% response rate of carboplatin. Based on these evidences, we have developed a new regimen consisting of paclitaxel, ifosfamide, and nedaplatin (PIN). The aim of the present phase II study was to evaluate the efficacy of the PIN combination in patients with recurrent advanced urothelial cancer who had received prior cisplatin-based chemotherapy.

## Patients and methods

### Patient selection

Patients with histologically confirmed urothelial cancer who relapsed after prior cisplatin-based chemotherapy were candidates for the present study. Eligibility criteria were as follows: (1) histologically confirmed urothelial cancer not curable by other second-line chemotherapy and/or radiotherapy; (2) Eastern Cooperative Oncology Group (ECOG)-performance status (PS) 2 or less; (3) life expectancy 3 months or more; (4) adequate hematopoietic function (absolute neutrophil count $>1{,}500/\mu$L and platelet count $>100{,}000/\mu$L), and liver function (AST/ALT concentrations less than two times the upper normal limit unless caused by tumor, and serum albumin level $>3.0$ g/dL); (5) absence of active coronary artery disease (in the form of unstable angina or myocardial infarction over the last 12 months), unstable diabetes mellitus, or peripheral neuropathy ≥ grade 2 by National Cancer Institute Common Toxicity Criteria (NCI-CTC); (6) presence of bidimensionally measurable disease. Informed consent was obtained from each patient before study entry according to institutional policies.

### Treatment schedule

Eligible patients were treated as follows: paclitaxel (Taxol; Bristol-Myers Squibb, Princeton, NJ, USA) was administered at 175 mg/m$^2$ over 3 h by intravenous (IV) infusion on day 1, after premedication consisting of dexamethasone 20 mg, diphenhydramine hydrochloride 50 mg, and ranitidine hydrochloride 50 mg; all were administered by 30-min IV infusion 1 h before paclitaxel. Ifosfamide (Ifomide; Shionogi, Osaka, Japan) was administered at 4.5 g/m$^2$ IV for 1 hour over a 3-day period (on days 1, 2 and 3, 1.5 g/m$^2$ per day; total dose, 4.5 g/m$^2$) together with mesna uroprotection, at 20% of the ifosfamide dose, given by IV infusion before and at 4 and 8 h after ifosfamide. Nedaplatin (Aqupla; Shionogi, Osaka, Japan) was administered at 70 mg/m$^2$ IV for 30 min on day 1 with adequate hydration.

Standard antiemetic medication included azasetron hydrochloride (Serotone) given 30 min before chemotherapy (at 10 mg IV) days 1, 2 and 3. Dexamethasone 20 mg IV was also administered 5 h after chemotherapy on days 1, 2 and 3, and after chemotherapy on days 4 through 6 (dexamethasone 4 mg tid orally). Hematopoietic growth factors included ganulocyte colony-forming factor (G-CSF) 2 μg/kg administered subcutaneously from the day when the WBC count was $1{,}000/\mu$L or less.

### Dose modifications for toxicity

The prerequisites for dose modifications were as follows: (1) any episode of grade 4 thrombocytopenia requiring platelet transfusion, (2) according to the impairment of renal function (24 h CCr) just before starting each cycle of PIN therapy.

The following guidelines were applied with respect to dose reductions for toxicity: (1) for thrombocytopenia, all drugs of PIN therapy was reduced by 25%. (2) For

renal toxicity, nedaplatin and ifosfamide were reduced as shown in Table 1. If the CCr dropped to less than 30 mL/min, nedaplatin was omitted in subsequent cycles.

If the blood counts had not recovered to an absolute neutrophil count of 3,000/$\mu$L and platelet count of 100,000/$\mu$L on the day of therapy, treatment was withheld until recovery.

### Pretreatment, follow-up studies, and response evaluation

Tumor measurements were performed by physical examination and a specific radiologic test that documented measurable disease before treatment. Clinical examinations, full blood counts, biochemical tests, and chest X-rays were carried out before each cycle of therapy. Blood counts were checked on days 4, 8, 12, and 16 after each cycle and until full recovery.

Complete response (CR) was defined as the disappearance of all signs and symptoms of disease for at least 1 month, with the documented disappearance of all-known lesions by physical examination, X-rays, computed tomography scans, and bone scans, and no new lesions. Partial response (PR) was indicated by a decrease of 50% or greater in the sum of the products of the two largest perpendicular diameters of all measurable lesions and no concomitant growth of new lesions for at least 1 month. There could be no deterioration of symptoms or performance status unless secondary to drug toxicity. Stable disease (SD) was indicated by a decrease of less than 50% or an increase in tumor size of less than 25% over the original measurements. There could be no deterioration of symptoms or performance status unless secondary to drug toxicity. Progressive disease (PD) was defined as an increase of 25% or greater over the original measurements, and relapse was documented if, after a period of response, a former lesion reappeared or enlarged as above or a new lesion appeared. Follow-up disease evaluation was performed at approximately 3-month intervals after the end of treatment.

### Statistical methods

Because the trial was designed as a phase II study, the primary objective of the study was the response rate (RR). Response duration was measured from the day of initial documentation until PD. One 3-day administration of chemotherapy was considered adequate for response assessment. We also evaluated time to progression (TTP) and overall survival (OS). TTP was calculated from the day of the initiation of treatment until the date of relapse, disease-related death before response evaluation, or last contact for patients without relapse at the time of analysis. Patients who died because of an unrelated disease and also without progression were examined at the time of the aforementioned events. OS was measured from the day of entry until the last follow-up or death. Survival curves of TTP and OS were produced with the Kaplan and Meier method [14] and compared between some categories with the log-rank test. Frequency distributions were used to describe the categoric variables, whereas continuous variables were presented as means and standard deviations. Differences across treatment arms regarding all categoric variables were examined with a chi-square test; for continuous variables the Mann–Whitney U test was used. Toxicity was evaluated at each chemotherapy visit according to National Cancer Institute Common Toxicity Criteria version 2. Throughout the analysis a level of 5% was used to show statistical significance.

**Table 1** Dose modification according to renal function

| | CCr (ml/min) | | | |
|---|---|---|---|---|
| | > 60 | 45–60 | 30–45 | < 30 |
| Nedaplatin | 100% | 75% | 50% | – |
| Ifosfamide | 100% | 80% | 75% | 70% |

## Results

### Patient characteristics

The characteristics of the 32 patients entered into this study are listed in Table 2. Histological examination of the primary tumor in all patients showed urothelial cancer (UC). Tumors initiated in the bladder in 11 patients, in the upper urinary tract in 17 patients, in both the bladder and upper urinary tract in 2, and in the urethra including the prostate in 2 patients. All patients received first-line cisplatin-based chemotherapy (M-VAC in 9, MEC in 22. and CISCA [Cisplatin, Adriamycin, and Cyclophosphamide] in 1), and the median time from the last chemotherapy cycle to the beginning of PIN was 5 months (range, 1–58 months). Initial chemotherapy was given as the adjuvant setting in 6 (19%) patients and for metastatic disease in 26 (81%).

### Response to treatment and survival

Among the 32 assessable patients, there were 5 CRs (16%) and 19 PRs (59%) for an overall RR of 75% (95% confidence interval [CI], 59–91%); there were also four cases of SD (13%) and four cases of PD (13%). The median TTP was 8 months (range, 0–50+ months). The median duration of survival for all patients was 22 months (range 4–52+ months). The 1- and 2-year overall survival rates were 53.7 and 42.9%, respectively (Fig. 1). We compared response rates with regard to responses to first-line cisplatin-based chemotherapy (Table 3). All six patients who had been treated in the adjuvant setting responded to PIN combination. The

**Table 2** Patient characteristics

| Characteristic | No. of patients ($N = 32$) | % |
|---|---|---|
| Gender | | |
| Male | 24 | 75 |
| Female | 8 | 25 |
| Age, years | | |
| Median | 66 | |
| Range | 41–77 | |
| ECOG-PS* | | |
| PS0 | 15 | 47 |
| PS1 | 12 | 38 |
| PS2 | 5 | 16 |
| 24 h-CCr (ml/min) | | |
| Mean ± SD | 62.2 ± 22.6 | |
| Range | 29–119 | |
| Response to first-line cisplatin-based chemotherapy | | |
| CR | 1 | 3 |
| PR | 13 | 41 |
| SD | 8 | 25 |
| PD | 4 | 13 |
| NE | 6 | 19 |
| Time to relapse after initial cisplatin-based chemotherapy | | |
| ≤ 6 months | 19 | 59 |
| > 6 months | 13 | 31 |
| Disease site | | |
| Lymph nodes | 24 | 75 |
| Lung | 6 | 19 |
| Bone | 5 | 16 |
| Liver | 2 | 6 |
| Soft tissue | 3 | 9 |
| Primary site | 5 | 16 |

*NE* Not evaluable (Chemotherapy in an adjuvant setting)

median time from the last cisplatin-based chemotherapy was 8.5 months (range, 5–23 months). The median duration of survival in these patients was 19 months (range, 7–50+ months). On the other hand, the response rate was 69% (95% CI, 51–88%) in 17 of 26 patients who had been treated with first-line cisplatin-based chemotherapy for metastatic disease. The median duration from the last chemotherapy was 3.5 months (range, 1–58 months). The median duration of survival after PIN combination in these patients was 22 months (range, 4–52+ months). Fourteen of 16 (88%) patients with tumors confined to the lymph nodes responded to PIN, as did 10 of 16 (63%) patients with extranodal metastases at the time of study entry. The response rate by each disease site is shown in Table 4. On the basis of ECOG-PS, the survival and response to the PIN combination for each of these categories are characterized in Table 5. A total of 142 treatment cycles were administered (median, 3.5; range 1–10), with a mean of 4.4 cycles per patient. While 71 (50%) of the total of 142 cycles in the present study were administered without dose reduction, in 71 cycles it was necessary to reduce the doses of nedaplatin and ifosfamide according the guidelines for dose reduction (Table 1). Twelve patients received the full dose of PIN combination (median 5 cycles; range, 3–10) and 20 patients required dose reduction (median 3 cycles; range, 1–9). Nine of 12 (75%) patients who were treated with the full-dose PIN combination obtained a CR or PR, as did 15 of 20 (75%) patients who required dose reduction of nedaplatin and ifosfamide.

### Toxicities

The hematologic and nonhematologic toxicities were evaluated by the NCI-CTC for all 19 patients and are shown in Table 6. Grades 3 and 4 neutropenia occurred in all patients and GCSF was given. Although febrile neutropenia occurred in 8 (25%) patients, all patients were managed successfully with broad-spectrum antibiotics and their pyrexia did not exceed 3 days. Grades 3 and 4 thrombocytopenia occurred in 8 (25%) patients and 2 patients classified as having grade 4 toxicity required platelet transfusion. Grades 3 and 4 anemia were observed in 6 (19%) patients. Grade 3 neuropathy occurred in 1 (3%) patient, who could not continue to receive additional cycles of PIN combination after 3 cycles. There were no differences in toxicity profiles between patients treated with full-dose PIN combination and those with dose reduction of nedaplatin and ifosfamide. There was no death as a result of treatment.

## Discussion

Several novel chemotherapeutic agents have been recently developed and identified to be effective in

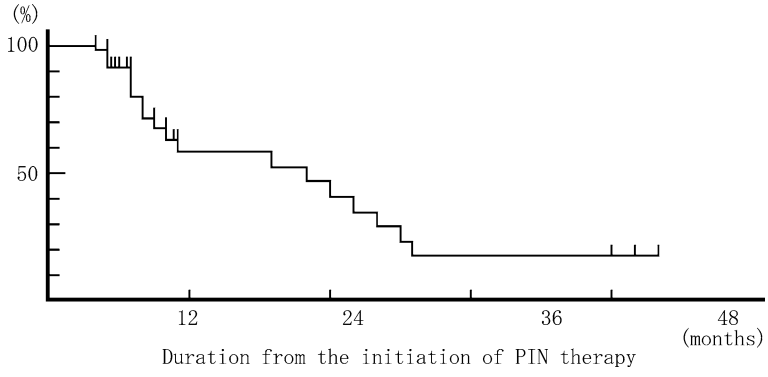


**Fig. 1** Actuarial survival curves of patients evaluated in the present study (Kaplan–Meier plot). *Tick marks* indicate surviving patients at the particular time points (censored)

**Table 3** Response according to response to first-line cisplatin-based chemotherapy

| Response to first-line chemotherapy | Response to PIN combination | | | |
|---|---|---|---|---|
| | *n* | CR (%) | PR (%) | OR(%) |
| CR | 1 | 0 (0) | 1 (100) | 1 (100) |
| PR | 13 | 3 (23) | 6 (46) | 9 (69) |
| SD | 8 | 1 (13) | 4 (50) | 5 (63) |
| PD | 4 | 0 (0) | 3(75) | 3 (75) |
| NE* | 6 | 1 (17) | 5 (83) | 6 (100) |

*CR* complete response, *PR* partial response, *SD* stable disease, *PD* Progressive disease, *OR* objective response, *NE* Not evaluable (chemotherapy in an adjuvant setting)

**Table 4** Response according to disease sites

| Disease site | *n* | CR (%) | PR (%) | OR (%) |
|---|---|---|---|---|
| Lymph nodes | 24 | 4 (17) | 13 (54) | 17 (71) |
| Lung | 6 | 1 (17) | 4 (67) | 5 (83) |
| Liver | 2 | 0 (0) | 1 (50) | 1 (50) |
| Soft tissue | 3 | 0 (0) | 3 (100) | 3 (100) |
| Primary site | 5 | 0 (0) | 2 (40) | 2 (40) |

*CR* complete response, *PR* partial response, *OR* objective response

**Table 5** Response and survival based on ECOG-PS

| Performance status | *n* | CR (%) | PR (%) | OR (%) | Median survival (months) range |
|---|---|---|---|---|---|
| 0 | 15 | 5 (33) | 8 (53) | 13 (86) | 30 (5–52+) |
| 1 | 12 | 0 (0) | 9 (75) | 9 (75) | 11 (6–48+) |
| 2 | 5 | 0 (0) | 2 (40) | 2 (40) | 7 (4–24) |

*CR* complete response, *PR* partial response, *OR* objective response

patients with metastatic urothelial cancer. In particular, paclitaxel appears to be very promising, its single-agent activity being at least as high as or even higher than that of cisplatin [9]. In expectation of enhanced anticancer activity, combinations of paclitaxel and other anticancer drugs have been investigated. In vitro studies demonstrated that paclitaxel intensifies the cell-killing effects of DNA damage chemically induced by alkylating agents, provided that it is given before these agents [15]. In the clinical setting, paclitaxel has shown enhanced activity and possibly synergistic effects when combined with cyclophosphamide or ifosfamide [16] or with cisplatin [17]. Therefore, it is expected that the combination of paclitaxel, ifosfamide, and cisplatin will have a favorable cytotoxicity profile against a variety of advanced solid tumors. Bajorin et al. reported that the combination of paclitaxel, cisplatin, and ifosfamide (ITP) was one of the most effective regimens against chemo-naïve advanced urothelial cancer [10]. In this phase II trial, a response rate of 68% was obtained in 44 assessable patients, with 10 (23%) patients achieving a CR. At a median followup of 28 months, the median survival was 20 months.

**Table 6** Common toxicities (worse adverse event)

| Toxicity | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|
| Granulocytopenia | | 6 (19%) | 26 (81%) |
| Thrombocytopenia | 5 (16%) | 6 (19%) | 2 (6%) |
| Anemia | 4 (13%) | 4 (13%) | 2 (6%) |
| Neuropathy | 9 (28%) | 1 (3%) | |
| Myalgia/Arthralgia | 3 (9%) | | |
| Fatigue | 1 (3%) | | |
| Alopecia | | 32 (100%) | |

In expectation of further enhanced anticancer activity, cisplatin was substituted for nedaplatin in ITP regimen. When we plan to perform salvage chemotherapy for patients with recurrent urothelial cancer who have undergone first-line chemotherapy, we should consider that urothelial cancers in these patients might have earlier acquired cisplatin resistance. Therefore, it is clearly necessary to overcome cisplatin resistance in previously treated urothelial cancer. Nedaplatin is a second-generation platinum complex developed in Japan and high activities against a variety of solid cancers, including advanced bladder cancer, have been reported [13, 18, 19]. In vitro studies demonstrated that 28% of cisplatin-resistant tumors were still sensitive to nedaplatin [20]. A phase I study demonstrated that the maximum tolerated dose and the recommended dose for phase II studies of nedaplatin was 120 and 100 mg/m$^2$, respectively, and the dose-limiting toxicity was thrombocytopenia [12]. Furthermore, ifosfamide has been shown to synergize with platinum compounds by reversing intracellular mechanisms of resistance that would ultimately lead to increased DNA repair and/or detoxification of reactive intermediates of platinum compounds, such as the glutathione/thiol systems. Depletion of the intracellular glutathione pool by 70% has been observed in peripheral-blood lymphocytes after ifosfamide administration [21]. It is thus theoretically conceivable that administration of ifosfamide and nedaplatin might overcome resistance to cisplatin due to elevated glutathione concentrations. Moreover, paclitaxel inhibits energy-dependent enzymatic reactions, by disengaging activated intracellular phosphate (ATP and GTP), required for the repair of the DNA damage induced by platinum derivatives [22]. In fact, a significant synergistic effect was obtained for paclitaxel and nedaplatin combination in preclinical mice tumor model [23] and in phase I trial for unresectable lung squamous cell carcinoma [24]. Thus, the combination of paclitaxel, ifosfamide, and nadaplatin appears to be capable of overcoming cisplatin resistance in recurrent urothelial cancer previously treated with cisplatin-based chemotherapy.

In the present study, we showed that the PIN regimen was a reasonable, logically implemented treatment for patients with recurrent urothelial cancer who has been treated with M-VAC or MEC. An overall response rate of 75% was observed, with a CR rate of 16%. The combination of gemcitabine and paclitaxel given every 2 weeks for salvage therapy for urothelial cancer was recently reported by Sternberg et al [25]; this was well tolerated and produced responses in 60% of patients. The combination of cisplatin, gemcitabine, and ifosfa-

mide was also tolerated and produced responses in 40.8% of previously treated patients with advanced urothelial cancer [26]. Furthermore, the median survival time of 22 months in the present study was longer than those observed in the phase II trials on the two-drug combination of paclitaxel and ifosfamide [27] or gemcitabine and paclitaxel [25] or the three-drug combination of cisplatin, gemcitabine, and ifosfamide [26].

The toxicity of this regimen was substantial, but not critical. Despite the high incidence of grade 4 neutropenia (81%) in the present study, it can be stated that this was rarely prolonged and patients were successfully managed with G-CSF. Although platelet transfusions were required in patients with grade 4 thrombocytopenia, there was no evidence of cumulative thrombocytopenia. Thus, no patient was dropped from this study because of hematologic side effects. Neurotoxicity was one of the dose-limiting factors for paclitaxel and one patient discontinued the PIN combination. These findings suggest that, although meticulous attention is needed because most patients are often elderly and their general status is poor, the PIN regimen is relatively well tolerated with a high response rate.

In conclusion, the PIN combination at the doses and schedule applied in the present study seems to be a very effective regimen for patients with recurrent advanced urothelial cancer who have previously received M-VAC or MEC and good performance status. Although the present study provides valid phase II data for PIN applied as a second-line treatment, the promising outcomes should be tested in a large-scale study.

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