Paclitaxel plus Doxorubicin Chemotherapy as Second-Line Therapy in Patients with Advanced Urothelial Carcinoma Pretreated with Platinum plus Gemcitabine Chemotherapy

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Schlüsselwörter
Paclitaxel · Doxorubicin · Fortgeschrittenes urotheliales Karzinom · Zweitlinientherapie

Zusammenfassung
Hintergrund: Die Effizienz und Toxizität von Paclitaxel plus Doxorubicin als Zweitlinientherapie bei Patienten mit urotheilaem Karzinom, die auf eine vorherige Behandlung mit einem Platin-Derivat plus Gemcitabin nicht angesprochen hatten, wurden retrospektiv bestimmt. Patienten und Methoden: Alle Patienten erhielten intravenöse Infusionen mit Paclitaxel (175 mg/m²/h) und Doxorubicin (50 mg/m²/30 min) an Tag 1. Chemotherapiekurse waren alle 21 Tage. Ergebnisse: Das mittlere Follow-up war 13.5 Monate (Spanne 2.8–22.4 Monate). Complete and partial responses wurden beobachtet in 2 (5.6%) and 10 (27.8%) Patienten, Residual median overall survival war 8.9 Monate (95% confidence interval (CI): 6.2–11.6). Median time to progression war 3.8 Monate (95% CI: 2.7–4.8). The most common hematologic toxicities were neutropenia (n = 21, 58.3%), thrombocytopenia (n = 10, 27.8%), and anemia (n = 9, 25%). The most common non-hematologic toxicities consisted of fatigue (n = 15, 41.7%), nausea/vomiting (n = 13, 36.1%), peripheral neuropathy (n = 11, 30.6%), and mucositis (n = 6, 16.7%). Dose reductions by 25–35% were performed in 6 (16.7%) patients because of grade 3/4 toxicity. Anthracyline-related heart failure did not occur. Conclusion: 3-weekly courses of cyclic paclitaxel plus doxorubicin were found to be effective and tolerable in patients with urothelial carcinoma, who had not responded to prior platinum- and gemcitabine-based chemotherapy.

Keywords
Paclitaxel · Doxorubicin · Advanced urothelial cancer · Second-line therapy

Summary
Background: We retrospectively evaluated the efficacy and toxicity of paclitaxel plus doxorubicin as a second-line treatment in patients with urothelial carcinoma, who had not responded to a prior platinum plus gemcitabine combination. Patients and Methods: All patients received intravenous infusions of paclitaxel (175 mg/m²/h) and doxorubicin (50 mg/m²/30 min) on day 1. Chemotherapy courses were repeated every 21 days. Results: The median follow-up duration was 13.5 months (range 2.8–22.4 months). Complete and partial responses were observed in 2 (5.6%) and 10 (27.8%) patients, respectively. Median overall survival was 8.9 months (95% confidence interval (CI): 6.2–11.6). Median time to progression was 3.8 months (95% CI: 2.7–4.8). The most common hematologic toxicities were neutropenia (n = 21, 58.3%), thrombocytopenia (n = 10, 27.8%), and anemia (n = 9, 25%). The most common non-hematologic toxicities consisted of fatigue (n = 15, 41.7%), nausea/vomiting (n = 13, 36.1%), peripheral neuropathy (n = 11, 30.6%), and mucositis (n = 6, 16.7%). Dose reductions by 25–35% were performed in 6 (16.7%) patients because of grade 3/4 toxicity. Anthracycline-related heart failure did not occur. Conclusion: 3-week courses of cyclic paclitaxel plus doxorubicin were found to be effective and tolerable in patients with urothelial carcinoma, who had not responded to prior platinum- and gemcitabine-based chemotherapy.
Introduction

Urothelial (transitional cell) cancer of the urinary tract is the 4th most common cancer among men, leading to 14,500 deaths annually [1]. The prognosis of patients with advanced urothelial carcinoma is generally poor, with a median survival of approximately 14 months despite optimal cisplatin-based chemotherapy [2]. During the last 2 decades, combination therapy with methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) has been the most common treatment regimen in patients with advanced or metastatic transitional cell carcinoma. However, since the M-VAC regimen is associated with significant toxicity, it is difficult to give to elderly patients who have a poor performance status [3]. A phase III trial comparing M-VAC with the combination of gemcitabine plus cisplatin (GC) demonstrated a similar efficacy with response rates (RRs) of 49 versus 46% and similar time intervals to disease progression (7.4 months in both arms) and median survivals (14.8 vs. 13.8 months) [4]. Similar efficacy with less toxicity in the GC arm was also confirmed for a 5-year follow-up period [2]. Since the GC regimen has less toxicity and similar efficacy, it is used worldwide more than the M-VAC regimen as first-line therapy in advanced or metastatic urothelial carcinoma.

For patients who have failed to respond to platinum- and gemcitabine-based chemotherapy, there is no standard chemotherapy regimen. If the duration of response is longer than 6 months, the use of the same regimen can be considered again. Alternatively, patients can be included in clinical trial-based therapies with novel agents. Although single-agent paclitaxel exhibited a 42% RR in untreated patients, it had a lower RR of 7% in patients who were refractory to prior chemotherapy [5, 6]. In 2 current studies, gemcitabine and paclitaxel have been used in combination as a second-line therapy in patients who did not respond to the M-VAC regimen. In these studies, objective response rates (ORRs) of 30 and 41.5% were reported [7, 8]. In the first phase II study that evaluated the role of anthracyclines in combination with paclitaxel as a second-line therapy, an ORR of 29% and median time to progression (TTP) of 7.6 months were reported. The indicated study revealed a significant benefit in the rates of both TTP and overall survival (OS) in patients with urothelial cancer, who had previously received cisplatin or carboplatin plus gemcitabine [9]. We evaluated the efficacy and toxicity of the paclitaxel plus doxorubicin as a second-line treatment in patients with urothelial carcinoma of the urinary tract, who had failed to respond to prior platinum plus gemcitabine combination therapy.

Patients and Methods

Patients

The medical records of 36 patients with advanced-stage urothelial (transitional cell) carcinoma, who had received paclitaxel plus doxorubicin chemotherapy as a salvage therapy between March 2006 and September 2011, were retrospectively evaluated. All patients had been previously treated with cisplatin or carboplatin plus gemcitabine as a first-line therapy. All patients had shown disease progression within 12 months following completion of the first-line therapy. Patients previously treated with anthracyclines and/or taxanes were excluded from the study. All patients had measurable or evaluable metastatic or unresectable locally advanced disease. Cardiac function of all patients was assessed by 12-lead electrocardiography and also echocardiography (normal left ventricular ejection fraction (LVEF) > 50%). Cardiac function was also evaluated by echocardiography at 2-monthly intervals. Inclusion criteria were as follows: Eastern Cooperative Oncology Group (ECOG) performance status 0–2, life expectancy of > 12 weeks, age 18–75 years, no previous malignant disease except for non-melanotic skin cancer, absence of concurrent uncontrolled medical illness, presence of adequate bone marrow (white blood cell count > 4,000/mm³ and or neutrophil count > 1,500/mm³, platelets > 100,000/mm³), liver (total bilirubin < 2 mg/dl, aspartate aminotransferase or alanine aminotransferase or aspartate aminotransferase < 3 times the upper limit of normal (ULN)) and renal function (blood urea nitrogen < 30 mg/dl, serum creatinine < 1.5 times ULN).

Treatment Plan

All patients received intravenous (iv) infusions of paclitaxel (175 mg/m²/h) and doxorubicin (50 mg/m²/30 min) on day 1. Chemotherapy courses were repeated every 21 days. We did not routinely use granulocyte colony-stimulating factor (G-CSF). A 5-hydroxytryptamin type 3 receptor antagonist, dexamethasone, and metloprolarmide were given as anti-emetic prophylaxis before every chemotherapy cycle. Before administration of paclitaxel, all patients received dexamethasone (16 mg iv), ranitidine (50 mg iv), and diphenhydramine (50 mg iv) in order to prevent drug-related hypersensitivity. Treatment was continued until the time to documented disease progression, unacceptable toxic effects, or patient refusal. Before starting treatment, all patients gave informed consent.

Evaluation of Therapeutic Response and Toxicity

Treatment-related toxicities were evaluated and graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0. Physical examination, complete blood counts, and biochemical analyses were performed after each cycle. In the event of grade 3 or 4 hematologic toxicity, the doses of both drugs were reduced by 25–35% in the next cycles. Chemotherapy cycles were delayed if on the day of infusion the patient’s absolute granulocyte or platelet counts were < 1,500/mm³ and 100,000/mm³, respectively. In cases of grade 3 or 4 non-hematologic toxicity other than alopecia (i.e. mucositis and peripheral neuropathy), doses of both drugs were reduced by 25–35% in the next cycles. The cardiac function of all patients was evaluated by echocardiography at 2-monthly intervals. Response to treatment was assessed after every 2 cycles by computed tomography of the abdomen and/or the thorax. Response was evaluated using RECIST (Response Evaluation Criteria In Solid Tumors) criteria. Therapeutic response was defined as complete (CR, disappearance of assessable disease) or partial response (PR, > 30% reduction of the 2 lesions with the largest diameters). Stable disease (SD) and progressive disease (PD) were defined as an increase in tumor size by < 25 and > 25%, respectively.

Statistical Analysis

TTP was estimated from the first day of treatment until disease progression or the last day of follow-up without disease progression. OS time was measured from the start of chemotherapy until death from any cause or
the date of the last follow-up. OS and TTP were assessed using the Kaplan-Meier method. SPSS version 17.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

Patient Characteristics

Characteristics of the patients and tumors are shown in table 1. The male/female ratio was 35/1, and the median age of the patients was 62 years (range 42–75 years). 51 (86.2%) patients had an ECOG performance status of 0 or 1; 5 (13.8%) patients had an ECOG status of 2. All patients had metastatic disease or unresectable locally advanced stage disease at the beginning of the treatment. In the first-line treatment, gemcitabine plus cisplatin (n = 30, 83.3%) or gemcitabine plus carboplatin (n = 6, 16.7%) regimens had been administered. In addition, platinum resistance was noted in all patients. Mostly, lymph nodes, liver, lung, and the skeletal system were affected.

Efficacy and Survival

The median follow-up period was 13.5 months (range 2.8–22.4 months). CR and PR were observed in 2 (5.6%), and 10 (27.8%) patients, respectively. SD and PD were observed in 5 (13.9%), and 19 (52.8%) patients, respectively. Total clinical benefit (CR+PR+SD) was observed in 17 (47.3%) patients. Median OS was 8.9 months (95% confidence interval (CI) 6.2–11.6) (fig. 1). Median TTP was 3.8 months (95% CI 2.7–4.8) (fig. 2).

Toxicity

The paclitaxel plus doxorubicin regimen was well tolerated and acceptable. A total of 143 cycles of chemotherapy were administered. The median number of chemotherapy cycles

![Fig. 1. Median overall survival (OS) was 8.9 months (95% confidence interval 6.2–11.6).](image)

![Fig. 2. Median time to progression (TTP) was 3.8 months (95% confidence interval 2.7–4.8).](image)
was 4 (range 1–8). Treatment-related toxicities are displayed in table 2. Grade 1/2 and 3/4 neutropenias were observed in 15 (41.72%) and 6 (16.7%) patients, respectively. Grade 1/2 thrombocytopenia was observed in 10 (27.8%) and grade 1/2 anemia in 9 (25%) patients. The most common non-hematologic toxicities consisted of fatigue (n = 15, 41.7%), nausea/vomiting (n = 13, 36.1%), peripheral neuropathy (n = 11, 30.6%), and mucositis (n = 6, 16.7%). Dose reductions by 25–35% were performed in 6 (16.7%) patients due to grade 3/4 toxicity. Anthracycline-related heart failure did not occur. During treatment, symptoms of heart failure did not appear. There were no toxicity-related deaths.

Discussion

We herein presented our clinical experience with paclitaxel plus doxorubicin combination chemotherapy in terms of efficacy and safety as second-line treatments for patients with advanced urothelial carcinoma. Median OS was 8.9 and median TTP 3.8 months. Total clinical benefit was observed in 17 (47.3%) patients, including an objective response in 12 (33.4%) patients.

There is no established standard treatment for patients with advanced urothelial cancer, who experience progression after first-line platinum-based regimens, and the search for second-line therapies in this setting has been a medical need. Single-agent paclitaxel has been investigated in several phase II trials. A study investigating weekly administration of paclitaxel (80 mg/m² iv) displayed an ORR of 10% with a median OS of 7.2 months. 77% of the patients enrolled in this study had visceral metastases, and only an RR of 26% to the first-line chemotherapy could be obtained [10]. However, in the other 2 trials that used single-agent paclitaxel, lower RRs of 7–9% were reported, with a median OS of 7 months [11, 12].

In the salvage setting, numerous single agents apart from paclitaxel have been evaluated in patients who were refractory to platinum-based chemotherapy. In these studies, RRs between 9 and 29% and median OS times ranging from 5 to 13 months depending on the characteristics of the enrolled patients were reported [13–18].

The role of prognostic factors for patients who need second-line chemotherapy was previously unexplored. In a current study reported by Bellmunt et al. [19], lower hemoglobin values, an ECOG performance status of ≥ 1, and the presence of liver metastases were established as independent prognostic factors for predicting shorter survival in patients with metastatic urothelial cancer, who had experienced treatment failure with prior platinum-based chemotherapy. This model may be used to predict outcome in patients before initiating a second-line regimen. The majority of patients in our study had several organ metastases other than liver. However, 5 patients had an ECOG performance status of 2. Due to the limited number of patients in our study, subgroup analysis was not performed for prognostic factors.

Recently, a semi-synthetic third-generation vinca alkaloid, vinflunine (VFL), was shown to improve OS by 2 months (6.9 months in the VFL plus best supportive care (BSC) arm vs. 4.6 months in the BSC only arm; p = 0.04) when compared with BSC alone. However, on adjusted multivariate analysis, addition of VFL to BSC was an independent prognostic factor for improved OS (p = 0.036) which reduced the risk of death by 23% (hazard ratio 0.77) [20].

Anthracycline is an active agent included in the M-VAC regimen used in the first-line treatment of urothelial cancer. We have retrospectively investigated the efficacy and safety of a paclitaxel plus doxorubicin combination in patients with urothelial cancer, who did not receive the M-VAC regimen in the first-line setting and failed to respond to platinum and gemcitabine combination chemotherapy.

Among the limited number of studies focusing on second-line chemotherapy for advanced urothelial carcinoma of the urinary tract, a recently published phase II trial evaluated the efficacy and toxicity of weekly administration of paclitaxel plus epirubicin in patients who deteriorated after platinum- and gemcitabine-based chemotherapy in the second-line setting. In that study, an ORR of 29% including SD in 23% of patients (ORR+SD: 52%), and a median OS of 12.6 months were reported. Toxicities in this study were of a mild and acceptable degree, while only 1 patient suffered from febrile neutropenia and only 3 patients had grade 3 peripheral neuropathy [9].

Unlike the above-mentioned study, in our study the paclitaxel plus doxorubicin regimen was used at 3-weekly intervals. In our study, median OS and median TTP were slightly shorter than those reported by Rozzi et al. [9] (12.6 and 7.6 months vs. 8.9 and 3.8 months, respectively), but the levels of toxicity in our study were comparable. The lower survival rates in our study may be associated with higher rates of extranodal involvement and enrolment of patients with an ECOG performance status of 2. In conclusion, in light of this retrospective study, 3-weekly paclitaxel plus doxorubicin could represent an interesting option in patients with urothelial carcinoma of the urinary tract, who have failed to respond to platinum- and gemcitabine-based chemotherapy.

Disclosure Statement

There is no conflict of interest.
Second-Line Therapy in Patients with Advanced Urothelial Carcinoma

References