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Gemcitabine and paclitaxel combination therapy in transitional cell carcinoma of the urothelium

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Abstract

Transitional cell carcinoma (TCC) of the urothelium is considered a chemosensitive malignancy; however, few patients receiving standard therapies achieve long-term disease control. Thus, new treatment approaches using more effective and less toxic agents are needed to improve prognosis in these patients. Two new agents currently being studied are gemcitabine and the taxanes; both of which have produced overall response rates ranging from 22.5 to 28% (gemcitabine), and 7–56% (paclitaxel) when used as single agents in this disease. Both agents have been well tolerated. Results of two phase II studies of gemcitabine combined with paclitaxel have been published. In one, 60% (15/25) of evaluable patients with advanced stage IV TCC responded; in the other, 53% (8/15) of patients with advanced and/or metastatic TCC responded. Several trials evaluating different dosing regimens of gemcitabine plus paclitaxel or docetaxel are ongoing or planned.

Keywords: Urothelial cancer; Transitional cell carcinoma; Gemcitabine; Paclitaxel

1. Introduction

Transitional cell carcinoma (TCC) of the urothelium is considered sensitive to chemotherapy; however, the disease remains essentially incurable, with only a small number of patients achieving long-term control of their disease. The only current treatment modality that provides potential for long-term survival in patients with metastatic TCC is systemic chemotherapy. Until recently, the most active single agents have been cisplatin and methotrexate, yielding overall response rates of 30–35% [1]. Thus, combination chemotherapy based on these agents has become the standard of care for patients with this disease. The most frequently used combination regimen of methotrexate, vinblastine, doxorubicin and cisplatin (M-VAC) has produced response rates of 39–72% [2–7] and median survival times of 12–13 months [8,9] in two phase III studies.

In a recent long-term study, however, only 3.7% of patients randomised to receive M-VAC were alive and continuously disease free at 6 years [10]. The M-VAC regimen is also associated with considerable toxicity, including myelosuppression, neutropenic sepsis, mucositis, nephrotoxicity, peripheral neuropathy and a toxic death rate of 3–4% [8]. Therefore, it is vital to develop more effective and less toxic drug regimens for patients with TCC of the urothelium. This is particularly important in the treatment of bladder cancer, a tumour which is found most frequently among elderly patients in poor general health. Their presentation is often further complicated by renal failure and, therefore, these patients might not benefit from treatment that includes cisplatin. In this regard, combination regimens that include gemcitabine and the taxanes (paclitaxel or docetaxel), new agents with promising single-agent activity against TCC, offer an encouraging alternative.

2. Gemcitabine and paclitaxel as single agents

Gemcitabine (2′2′-difluorodeoxycytidine; dFdC) is an antimetabolite that inhibits DNA synthesis and ribonucleotide reductase. Gemcitabine requires activation by deoxycytidine kinase and other kinases to its triphosphate, which can then be incorporated into RNA and DNA. The latter effect causes masked-chain termination and inhibition of DNA repair, and is considered responsible for the antitumour activity of gemcitabine [11].

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In phase II studies of chemonaïve and previously treated patients, including prior platinum therapy, gemcitabine monotherapy resulted in response rates ranging from 22.5 to 28%. Overall toxicity was mild, predominantly myelosuppression, which is the usual dose-limiting toxicity [12–14].

The taxanes represent a novel class of antineoplastic drugs. Paclitaxel and docetaxel share a similar mechanism of action: the promotion of microtubule assembly and inhibition of microtubule disassembly [15]. In previously untreated patients with advanced urothelial carcinoma, single-agent paclitaxel as a 24-h infusion produced an overall response rate of 42% [16]. In a small study of 9 untreated patients with renal insufficency, single-agent paclitaxel, also given as a 24-h infusion, resulted in a response rate of 56% [17]. In patients with advanced TCC of the bladder who were refractory to previous chemotherapy, single-agent paclitaxel produced a response rate of 7% [18]. To date, these three studies are the only published studies of single-agent paclitaxel in bladder cancer. Single-agent docetaxel produced only a 13% response rate in patients refractory to cisplatin-based therapy [19]. However, as first-line therapy, single-agent docetaxel produced response rates of 31% [20] and 45% [21], respectively. Patients in the latter study had impaired renal function. Both paclitaxel and docetaxel were well tolerated in these patients.

Based on the documented activity and tolerability of gemcitabine and the taxanes as single agents against metastatic urothelial cancer in both untreated patients and patients refractory to current cisplatin-based regimens, these agents have been explored further as combination therapy in the treatment of this disease. Thus far, the results of two phase II studies are published.

3. Published phase II studies of gemcitabine plus paclitaxel therapy

Meluch and colleagues [22] enrolled a total of 26 patients (19 male, 7 female) with advanced TCC (all stage IV disease) in a study of gemcitabine plus paclitaxel. The median patient age was 66 years (range: 33–88 years). Eligible patients were allowed to have one previous systemic chemotherapy treatment, and all had adequate haematological and organ function. World Health Organization (WHO) (Zubrod) performance status was 0–1 in 21 of the patients, and was 2 in the other 5 patients. Patients received paclitaxel 200 mg/m^2 intravenously (i.v.) over 1 h on day 1 and gemcitabine 1000 mg/m^2 i.v. on days 1, 8 and 15, every 21 days. Chemotherapy continued for a maximum of six cycles. Patients were administered a total of 103 treatment cycles (median: 4 cycles; range: 1–6 cycles). Reasons for not completing six cycles of therapy included progressive disease ($n=10$), paclitaxel hypersensitivity reaction ($n=1$), death from an unrelated cause ($n=1$) and death related to infection ($n=1$). The remainder of the patients are still on study. One patient had not yet completed two treatment cycles and was therefore not available for evaluation. Among 25 evaluable patients, 15 responded (overall objective response rate = 60%) with 2 complete responses and 13 partial responses. Among the 15 responders, 12 (80%) had not received previous treatment compared with 3 responders amongst 10 patients who had previously received platinum-based combination regimens, including cisplatin-based regimens (all M-VAC) in 7 patients and carboplatin-based regimens similar to M-VAC in 3 patients. The complete evaluation of sites of disease and response by site of disease had not been finalised by the time of this report. Median follow-up and duration of response also have not yet been analysed. Principal toxicities involved myelosuppression with grade 3/4 neutropenia and thrombocytopenia in 50% and 19% of patients, respectively. 5 (19%) patients were hospitalised for neutropenic fever, although no bleeding was reported. Two patients (8%) developed grade III/IV neuropathy. This ongoing study has not completed patient accrual and follow-up is continuing. The schedule of this regimen with no week of rest may have contributed to the haematological toxicities, although the majority of the day 1 and 8 doses were received. An upcoming trial with this combination will consider omission of the day 15 dosing of gemcitabine.

In a study conducted by Marini and colleagues [23], 16 patients (14 males, 2 females; median age 67 years, range: 54–76 years) with advanced and/or metastatic TCC who had previously received one or more cisplatin-containing regimens were treated with gemcitabine 2500–3000 mg/m^2 i.v. over 30 min and paclitaxel 150 mg/m^2 i.v. over 3 h, every 2 weeks. Granulocyte colony-stimulating factor was given on days 3–9 for haematological toxicity greater than grade 3. There was no limitation on treatment duration. The median number of administered treatment cycles was 8 (range: 2–14). Forty-four per cent of patients had abdominal/pelvic masses and 56% had lymph node involvement (78% retroperitoneal, 44% mediastinal, 33% pelvic). Results showed an overall response rate of 53% amongst 15 patients with bidimensionally measurable lesions, with 3 complete responders and 5 partial responders. 2 patients achieved stable disease. One patient with evaluable bone only disease had a marked reduction in bone pain for 4 months. The median response duration was 6.2 months (range: 4–12+). One patient with a partial response in the liver died due to gastrointestinal bleeding and leucopenic sepsis in the 14th treatment cycle. All patients had alopecia. Other grade 3/4 toxicities included neutropenia in 7 of 16 patients (44%) and neurotoxicity in 1 patient (6%).

4. Ongoing and planned phase II studies of gemcitabine plus paclitaxel therapy

Table 1 shows ongoing and planned studies of gemcitabine plus paclitaxel and gemcitabine plus docetaxel using six different dosing schedules in patients with advanced TCC.

5. Conclusions

Combinations of gemcitabine and the taxanes offer a promising treatment option for TCC of the urothelium based on the significant independent clinical activity against this disease, as well as the different mechanisms of action and resistance of the agents. Available phase II data demonstrate that gemcitabine in combination with paclitaxel is an active and tolerable regimen with minimal overlapping toxicities in patients with primary or recurrent TCC including prior platinum-treated patients. The 3-week and 2-week schedules are both feasible in these patients. Data regarding the gemcitabine plus docetaxel combination are not yet available. Mature phase II data and data from randomised trials are needed to determine the future role of gemcitabine plus taxanes in the treatment of patients with TCC.

Table 1
Planned/ongoing studies of gemcitabine plus taxanes in advanced transitional cell carcinoma of the urothelium

Investigator	Institution	Regimen
G. Pizzocaro	Instituto Nazionale Tumori Italy	Gem 3000 mg/m^2 Pac 150 mg/m^2 Day 1 Every 2 weeks
S. Srinivas	Veterans Affairs Medical Center Palo Alto USA	Gem 1000 mg/m^2 Pac 110 mg/m^2 Days 1, 8 and 15 Every 4 weeks
L. Einhorn	Hoosier Oncology Group USA	
S. Ebbinghaus	University of Alabama at Birmingham USA	Gem 1000 mg/m^2 Days 1 and 8 Pac 175 mg/m^2 Day 1 Every 3 weeks
A. Meluch	Sarah Cannon Cancer Center USA	Gem 1000 mg/m^2 Days 1, 8 and 15 Pac 200 mg/m^2 Day 1 Every 3 weeks
B. Gitlitz	University of California Los Angeles School of Medicine USA	Gem 800 mg/m^2 Days 1, 8 and 15 Doc 60 mg/m^2 Day 1 Every 4 weeks

Gem, gemcitabine; Pac, paclitaxel; Doc, docetaxel.

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