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Clinical report

Paclitaxel as weekly second-line therapy in patients with advanced pancreatic carcinoma

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Although the prognosis for patients with pancreatic adenocarcinoma is still poor, gemcitabine has shown significant impact upon survival and quality of life. Our aim was to examine the potential effectiveness of a second- or third-line therapy with paclitaxel (Taxol®) after confirmed progression with a gemcitabine-containing schedule for patients remaining in good clinical condition. Eighteen patients with stage IVb disease participated in this study. Pretreatment with gemcitabine was performed either as monotherapy and/or in combination with 5-fluorouracil (5-FU) and folic acid (FA). Paclitaxel was administered at weekly intervals on an outpatient basis. We observed 238 weekly treatments with a median number per patient of 12 treatments. The median dosage was 73 mg/m^2 paclitaxel (range 55–88 mg/m^2). Regarding toxicity, only one patient each presented with anemia and leukocytopenia of WHO grade III. Hepatotoxicity with a temporary increase in aminotransferase of WHO grade II occurred in three patients. Higher-grade symptomatic toxicity was rare, except alopecia. At this time, the median survival time is 17.5 weeks (range 7–88 weeks) since the start of therapy. Stable disease was observed in five patients. One patient achieved complete remission within 37 weeks. At this time, he has survived for more than 56 weeks after confirmed progression under first-line therapy. In conclusion, this schedule demonstrates that weekly therapy with paclitaxel after pretreatment can be effective with a low toxicity profile. This opens up an additional therapeutic option for a selected patient group with a poor prognosis so far. [© 2000 Lippincott Williams & Wilkins.]

Key words: Advanced pancreatic carcinoma, paclitaxel, pretreatment with gemcitabine, salvage therapy, weekly schedule.

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Introduction

Pancreatic carcinoma is the fifth most frequent cause of tumor-related deaths in the western world and thus responsible for 5% of all tumor-related deaths. With a continued rising trend, the incidence in men and women has more than doubled to 9 and 5.7, respectively, per 100 000 within the last 40 years. The prognosis of pancreatic carcinoma is very poor, as it is often diagnosed late. Only 5–10% of all patients can be admitted to potentially curative surgery. Palliative chemotherapy is one option for patients with advanced pancreatic carcinoma. Studies with the pyrimidine antimetabolite gemcitabine showed significant better improvement of tumor-related clinical symptoms, and a longer median and 1-year survival compared to 5-fluorouracil (5-FU).[1] Consequently, gemcitabine could be considered to be standard treatment for this tumor entity. Currently, further optimization of the therapeutic results is being studied in several studies in which gemcitabine is combined with other cytostatics.[2,3]

Usually, palliative chemotherapy is discontinued with confirmed progression after first-line treatment due to rapid deterioration in patients with pancreatic cancer. Therefore only very few studies have investigated second-line chemotherapy in pancreatic cancer so far.

Paclitaxel, a semisynthetic taxane, shows clinical activity in a multitude of solid tumors. It is a potent chemotherapeutic agent that interferes with mitotic spindles and thus inhibits the depolymerization of microtubules; this 'stabilization' blocks the mitotic cell cycle.[4] Clinical studies have demonstrated remission rates between 0 and 20% after treatment of patients with pancreatic carcinoma in 3-weekly sequences with both paclitaxel or docetaxel[5,6].

We report our experience with paclitaxel as second- or third-line chemotherapy in patients with pancreatic

cancer who progressed during gemcitabine-based chemotherapy.

Patients and methods

Patients with histologically confirmed pancreatic cancer were offered paclitaxel after progression as assessed computerized tomography (CT) or magnet resonance tomography (MRT) according to WHO criteria.

First-line treatment consisted of 1000 mg/m^2 gemcitabine (Gemzar®; Eli Lilly, Indianapolis, IN), administered as a 30-min infusion, either as monotherapy or in combination with 5-FU and folinic acid (FA). The combination followed the schedule of a previous phase I/II study in patients with inoperable pancreatic carcinoma.[3] In this schedule, gemcitabine was followed by 200 mg/m^2 FA (Rescuvolin®; Medac, Hamburg, Germany) administered over 2 h. A portable battery-driven pump (Walkmed 300) was used to administer 5-FU (750 mg/m^2) as a 24-h continuous infusion on days 1, 8, 15 and 22 of a 42-day schedule.

Consequently, patients were treated with one of the three possible therapeutic sequences:

(1) Pretreatment with gemcitabine as monotherapy; paclitaxel as second-line therapy (two patients).
(2) Pretreatment with a combination of gemcitabine, FA and 5-FU; paclitaxel as second-line therapy (12 patients);
(3) Pretreatment with gemcitabine as monotherapy followed by the combination of gemcitabine, FA and 5-FU; paclitaxel as third-line therapy (four patients).

Paclitaxel (Taxol®; Bristol-Myers Squibb, Sermoneta, Italy) was given at a dosage of 50 mg/m^2, diluted in 500 ml 0.9% NaCl solution over 90 min. The dosage was increased up to 85 mg/m^2 body surface area in the case of WHO toxicity less than grade III. Therapy was given on an out-patient basis weekly for 6 consecutive weeks with a break in week 7. All patients received an antiemetic medication of 50 mg alizapride, and an antiallergic prophylaxis with H_1 and H_2 antagonists (2 mg clemastine and 200 mg cimetidine) as well as 12 mg dexamethasone i.v. 30 min before starting therapy with paclitaxel.

Results

Eighteen patients (11 male and seven female) with a median age of 59 years (range 46–71) received 238 weekly treatments with paclitaxel. The median

Table 1. Patient characteristics

No. of patients	18
Male	11
Female	7
Median age (range)	59 (46–71) years
Karnofsky PS (range)	80% (70–100%)
Stage at beginning of therapy with paclitaxel (UICC 1997)	
IVa	0
IVb	18
Stage at beginning of therapy with gemcitabine (UICC 1997)	
III	2
IVa	6
IVb	10
Scheme of pretreatment	
gemcitabine monotherapy, paclitaxel second line	2 patients
Combination gemcitabine/FA/5-FU, paclitaxel second line	12 patients
gemcitabine monotherapy + combination, paclitaxel third line	4 patients
Median duration of pretreatment until confirmed progression	34 weeks

Table 2. Toxicities

Hematotoxicity	Maximum WHO grade	No. of patients
Total hematotoxicity	none	3
	I	8
	II	5
	III	2
Thrombocytopenia	none	16
	I	0
	II	2
Leukocytopenia	none	13
	I	2
	II	2
	III	1
Anemia	none	4
	I	9
	II	4
	III	1

Symptomatic toxicity	No. of patients	No. of weeks on therapy
Drug fever WHO I/II°	1	6
Nausea/vomiting WHO I/II°	2	
Diarrhea		
WHO I/II	2	10
WHO III	1	1
Obstipation	2	7
WHO I/II	1	3
WhO III	1	1
Onychodystrophy WHO I/II	3	
Cutaneous toxicity WHO I/II	2	
Alopecia WHO II/III	all patients with a longer duration of therapy	
Fatigue WHO I/II	7	

number of applications per patient was 12 (range 1–33) and the median duration of treatment was 14 weeks (range 1–63). Paclitaxel dosage could be increased to a median of 73 mg/m^2 (range 55–88) body surface area.

All 18 patients were assessable for toxicity evaluations. In general, hematotoxicity was mild. Only one patient each presented with anemia and leukocytopenia of WHO grade III (Table 2). The patient with anemia also suffered from gastrointestinal bleeding. In total, the administration of packed human red cells was necessary in six cases during all treatment cycles. A febrile episode of pneumonia occurred in connection with grade II leukopenia.

WHO grade II hepatotoxicity with a temporary increase in aminotransferase occurred in three patients. One patient with marked hepatic metastasis had grade IV hepatotoxicity. A dosage reduction by 30 mg was followed by a rapid decrease of aminotransferase. A rise in alkaline phosphatase grade IV was observed in connection with a partial occlusion of the choledochal stent.

Higher-grade symptomatic toxicity was very rare. Only one patient each had grade III diarrhea or obstipation. All patients with a treatment duration of several weeks suffered from alopecia grade II/III. Seven patients reported increased fatigue and others suffered from temporary somnolence. There was no grade III or IV neurotoxicity at all.

All 18 patients presented with a metastatic stage of disease at the beginning of salvage therapy. Four patients are still alive at this time. Current median survival time is 17.5 weeks (range 7–88 weeks) or more than 4 months (up to 22 months) since the beginning of therapy with paclitaxel. The median survival time of the total therapeutic sequence since start of first-line therapy is 12.3 months (range 5–44).

Fourteen of 18 patients received treatment for at least 10 weeks. CT/MRT evaluation of eight of 14 patients revealed disease progression. Stable disease was observed in five patients. One patient with marked peritoneal carcinomatosis achieved partial remission within 24 weeks and complete remission [confirmed by MRT, PET and tumor marker CA 19-9 (reduction from more than 100 U/ml to normal values] occurred within 37 weeks. At this time, he has survived for more than 56 weeks.

Regarding the tumor marker CA 19-9, we observed a reduction by at least 50% in three patients. A minor decrease of 25% occurred in another patient. Four patients had stable marker concentrations; a clear increase of the marker was observed in five patients. It must be emphasized that all patients showed a clear increase of CA 19-9 levels while progressing under first-line therapy.

Discussion

The present case observation with a weekly schedule of paclitaxel as salvage therapy for patients with locally advanced or metastatic pancreatic carcinoma pretreated with gemcitabine demonstrates that paclitaxel is active in this tumor entity. Following first-line chemotherapy, we observed a median total survival of 17.5 weeks and a progression-free interval of at least 10 weeks (confirmed in CT or MRI scan) in 33% of all patients, including one patient with complete remission. In this respect, it must be emphasized that paclitaxel was effective in advanced pancreatic carcinoma—despite previous statements that it has no effect at all on this tumor entity.[4] The treatment was generally well tolerated and hematotoxicity was mild. It is remarkable that none of our patients had to be admitted to hospital due to treatment-related symptoms during all 238 cycles. None of the patients in the present trial had WHO grade IV haemotoxicity and only two patients (11%) out of 18 suffered from grade III hematotoxicity. In conclusion, this second- or third-line schedule seems to be active and feasible for this certainly selected group of patients maintaining good performance status after progression under first-line chemotherapy with gemcitabine.

Comparative data analyzing the efficacy of weekly treatment schedules are rare. In a study by Löffler *et al.*,[9] 50 patients with different tumor entities were treated with weekly 1-h infusions of up to 90 mg/m^2 paclitaxel over 6 weeks. Two of four patients with advanced pancreatic carcinoma showed partial remission after dose-densified administration of paclitaxel, indicating that this treatment has an impact on this tumor entity.

The recent Hannover trials by Lück *et al.*[7] comparing the effects of paclitaxel and docetaxel in anthracycline-pretreated patients suffering from metastatic breast cancer also confirm that weekly applications of taxanes are well tolerated. By contrast with paclitaxel, only docetaxel was associated with grade III/IV gastrointestinal complications and painful nail disorders. In a large phase II study with paclitaxel administered as a weekly 1-h infusion in 130 patients with metastatic breast cancer evaluated to date only 6% developed grade III/IV anemia and 17% experienced grade III/IV myelosuppression. Overall, the toxicities were well tolerated by this population.[8]

There is only very little data on second-line therapy of pancreatic carcinoma available. Rothenberg *et al.*[10]

found a median survival of 3.9 months after second-line treatment with gemcitabine following first-line therapy with 5-FU. A similar period of survival could be demonstrated in our patients using paclitaxel after gemcitabine-based treatment. The median total survival time of more than 12 months after sequential treatment in the present trial was distinctly longer than the survival time reported after therapy with gemcitabine or taxanes alone. In our opinion, this success justifies a shift in therapy in patients showing progression during gemcitabine-based chemotherapy. By that, it should be mentioned that the median duration of pretreatment until confirmed progression was already 34 weeks and there certainly was a selection of patients maintaining good performance status.

In conclusion, we have found that the weekly administration of paclitaxel after pretreatment with gemcitabine-containing regimens in patients with advanced pancreatic carcinoma is well tolerated and can be effective. This indicates that a sequential treatment may be useful in these patients. A remarkable complete remission in one patient shows that weekly paclitaxel may achieve an even better success in the treatment of this tumor. The toxicity was low compared to previous treatment schedules and other regimens. The results open up an additional therapeutic option for a group of patients with pancreatic carcinoma maintaining good performance status while progressing under gemcitabine-containing chemotherapy. Therefore, this second-line scheme should be evaluated further in the framework of a large prospective phase II study.

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