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Short Communication

Phase I Study with a Weekly 1 h Infusion of Paclitaxel in Heavily Pretreated Patients with Metastatic Breast and Ovarian Cancer

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Paclitaxel has proven to be an active agent in the treatment of breast and ovarian cancer [Seidman AD, *Ann Oncol* 1994, 5 (Suppl. 6), 17–22], but the optimal dose and schedule remain undefined. We performed a phase I study with a weekly 1 h infusion of paclitaxel. After premedication, patients received a 1 h infusion of paclitaxel on days 1, 8, 15, 22, 29 and 36 (every 50 days) using the following dose levels: dose level 1 70 mg/m², dose level 2 80 mg/m², dose level 90 mg/m², dose level 4 100 mg/m². 20 patients (17 breast, 3 ovarian cancer) with anthracycline- or platinum-refractory disease entered this trial. No dose limiting toxicities occurred at dose levels 1–3. 2 of the 4 patients at dose level 4 had neutropenia WHO grade 4. At all dose levels responses could be observed. Maximal tolerable dose (MTD) was reached using dose level 4. Paclitaxel, given in a weekly 1 h infusion, is safe and shows mild toxicity in heavily pretreated breast and ovarian cancer patients. We recommend dose level 3 for phase II studies.

Key words: phase I, paclitaxel, 1 h infusion, breast cancer, ovarian cancer
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INTRODUCTION

PACLITAXEL is one of the few newer drugs which exhibit clinical relevant activity in various important tumour entities. The clinical development of the drug [1, 2] has led to different administration schedules including 1 –3 h and 24 h infusions every 3 weeks [3]. Meanwhile paclitaxel is under investigation in combination chemotherapy, although its optimal dose and time schedule still remain to be defined.

Considering the cellular mode of action of paclitaxel [4, 5], which is predominantly cytotoxic for dividing cells, repeated doses should be meaningful. This was the background for a phase I trial with a weekly schedule of paclitaxel in intensively pretreated breast and ovarian cancer patients.

PATIENTS AND METHODS

Inclusion criteria

Patients in this study had either anthracycline-resistant breast or platinum-resistant ovarian cancer. Other inclusion criteria were: progressive measurable or evaluable lesions, age ≤75 years, WHO performance status ≤2, life expectancy of ≥3 months, adequate renal, liver and bone marrow function. All patients gave their informed consent.

Staging and follow-up

Prior to treatment, all patients underwent complete medical history and physical examination, ECG, determination and measurements of study parameters by chest X-ray, bone scan, computer tomography (CT) scan and/or ultrasound. During treatment, patients had weekly full haematological blood counts, determination of liver and renal functions and assessment of non-haematological toxicities. Response to treatment was assessed prior to each cycle. The standard WHO criteria were used for evaluation of toxicities and response.

Treatment schedule

Paclitaxel was given as a 1 h infusion on days 1, 8, 15, 22, 29 and 36 representing one treatment cycle. The cycle was repeated every 50 days. All patients were treated under outpatient conditions. The premedication consisted of dexamethasone (8 mg oral 12 and 6 h prior to each paclitaxel infusion) and cimetidine (400 mg i.v.) and clemastine (2 mg i.v.) 30 min before each treatment with paclitaxel.

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Table 1. Frequency of toxicities (n) *in single weekly doses (SWD) per dose level*

	Dose levels							
	1 ($n = 8$, 131 SWD)		2 ($n = 5$, 57 SWD)		3 ($n = 3$, 61 SWD)		4 ($n = 4$, 48 SWD)	
WHO grade	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4
Neutropenia	7	—	—	—	1	1 (grade 3)	6	2 (grade 4)
Anaemia	—	—	—	—	—	—	—	—
Thrombopenia	—	—	—	—	—	—	—	—
Nausea/vomiting	2	—	—	—	2	—	—	—
Myalgia	2	—	—	—	1	—	1	—
PNP	4	—	2	—	6	—	2	2 (grade 3)
Diarrhoea	1	—	1	—	1	—	—	—
Mucositis	3	—	3	—	4	—	2	—
HSR	—	—	—	—	—	—	—	—

PNP, peripheral neuropathy; HSR, hypersensitivity reaction.

Dose escalation

The following dose levels were chosen: dose level 1 (starting dose) 70 mg/m^2, dose level 2 80 mg/m^2, dose level 3 90 mg/m^2, dose level 4 100 mg/m^2. No individual dose escalation was allowed at a given dose level. Paclitaxel was administered if no dose limiting toxicities (DLT) were present on the day of treatment. DLT were defined as: neutropenia grade 4, anaemia and thrombopenia ≥grade 3, other organ toxicity, except alopecia >grade 2 according to WHO criteria. In the case of DLT, treatment was postponed until full recovery of all side-effects and then continued using the next lower dose level. A minimum of three patients were treated at each dose level. If no DLT occurred, the next 3 patients entered the next dose level. If 1 of the 3 patients at a given dose level experienced DLT, 3 additional patients had to be entered. MTD was reached if DLT occurred in 2 of the 6 patients at one dose level.

Patient characteristics

20 patients with advanced breast cancer ($n = 17$) and advanced ovarian cancer ($n = 3$) entered this study. The median age was 54 years (range 32–73), the median performance status according to WHO criteria was 1 (range 0–1). Patients had bidimensionally measurable disease and a median of 2.7 metastatic disease sites (range 1–4).

Pretreatment characteristics consisted of a median of 2.6 chemotherapy regimens for advanced disease (range 1–4). All breast cancer patients had anthracycline-resistant disease and ovarian cancer patients platinum-resistant disease. 19 of the 20 patients had received radiotherapy (chest wall, bone metastases) prior to study entry.

RESULTS

All patients experienced alopecia WHO grade 3. No DLTs were seen in 8, 5 and 3 patients treated at dose level 1 [131 single weekly doses (SWD)], dose level 2 (57 SWD) and dose level 3 (61 SWD), respectively (Table 1). At dose level 4, 3 of the 4 patients had DLTs. 2 developed grade 4 neutropenia after the second application of paclitaxel, another patient suffered from grade 3 peripheral neuropathy (PNP) after the fifth week of treatment and was withdrawn. This patient had a pre-existing PNP WHO grade 1 after pretreatment with cisplatin for ovarian carcinoma. Within 3 weeks after stopping treatment with paclitaxel, PNP returned to grade 1. The MTD as defined was reached using dose level 4. The dose intensity of paclitaxel administered weekly at 90 mg/m^2 was 85 mg/m^2/wk.

Using the reduced premedication programme in order to avoid corticosteroid side-effects, it must be emphasised that neither mild nor severe hypersensitivity reactions occurred in dose levels 1–4. Additionally, no major corticosteroid side-effects were observed.

All patients had a defined progression of their disease according to WHO criteria prior to study entry. Of the 20

Table 2. Study treatment results

Dose level	Dose (mg/m^2)	No. of patients (n)	SWD (n)	Treatment delay (weeks)	Dose intensity (mg/m^2/week) during first 6 weeks of treatment	Time to progression [weeks (range)]	Response
1	70	8	131	—	70	16.5 (5–36+)	PD1, SD6, PR1
2	80	5	57	—	80	16 (3–24+)	PD3, SD1, PR1
3	90	3	61	1	85	20.3 (2–39+)	PD1, SD1, MR1
4	100	4	48	6	92	12 (6–24)	PD2, SD1, MR1

PD, progressive disease; SD, stable disease; MR, minor remission; PR, partial remission; SWD, single weekly doses.

patients treated, 2 had partial remissions, 2 minor remissions, 9 stable diseases and 7 progressive disease. Responses were observed at all dose levels (Table 2). The median time to progression for the whole study population was 14.9 weeks. 3 patients are still on treatment: one patient at dose level 1 with 36 SWD of paclitaxel and stable disease; 1 patient at dose level 2 with 24 SWD of paclitaxel and a partial remission and 1 patient at dose level 3 with 39 SWD of paclitaxel, who achieved a minor remission of the disease. An improvement of tumour related symptoms (pain, dypsnoea, weight loss) was seen in all patients with an objective tumour response and in 90% of patients with stable disease.

DISCUSSION

Current clinical experience indicates that the duration of paclitaxel infusion as well as the dose administered influence toxicity and efficacy. Compared with 24 h infusions of paclitaxel, 3 and 1 h infusions appear to be less myelotoxic but possibly also less active [6].

Based on theoretical considerations, and our own *in vitro* data, which support a more frequent administration of paclitaxel as compared to once every 3 weeks schedules, this phase I trial was done in order to determine the MTD (maximal tolerable dose) of a weekly paclitaxel schedule, and to determine whether a high dose intensity can be achieved without increasing side-effects.

The results of this trial show that a once a week six weekly administration of paclitaxel can safely be administered as an outpatient treatment. It is only associated with mild to moderate toxicities when paclitaxel is used in doses of 90 mg/m^2. This is also the dose which is recommended for phase II trials. The dose intensity of paclitaxel achieved with this weekly administration was 85 mg/m^2/week and markedly higher than 3 h infusion every 3 weeks (57 mg/m^2/week).

The first experiences with weekly paclitaxel in heavily pretreated and anthracycline-refractory breast cancer patients also indicate clinical activity. Nevertheless, further evaluation in phase II/III trials of the weekly paclitaxel schedule is needed to define better its clinical value as a single agent treatment and within combination chemotherapy.

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