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Schedule-dependent paclitaxel tolerance/activity: data from a 7 day infusion phase I study with pharmacokinetics in paclitaxel refractory ovarian cancer

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Our objective was to determine the maximum tolerated dose (MTD) of paclitaxel when given as a 7 day continuous i.v. infusion, repeated every 3 weeks, and to evaluate the toxicity and the efficacy of such a schedule of administration as a salvage treatment in ovarian cancer patients pretreated and refractory to 3 or 24 h paclitaxel. Thirteen women were enrolled in this phase I trial. Four dose levels ranging from 105 to 157.5 mg/m^2/cycle were explored. Two of four patients experienced dose-limiting febrile neutropenia at the dose of 157.5 mg/m^2. No objective response was observed, although three patients experienced disease stabilization (five to six cycles), with regression of disease symptoms, two of them having sustained 50% or greater decrease in CA 125. We conclude that the MTD in this population was paclitaxel 140 mg/m^2/7 days. Schedule-dependent mechanisms of resistance to paclitaxel could not be demonstrated in this clinical setting of heavily pretreated ovarian cancer patients.

Key words: Continous infusion, ovarian cancer, paclitaxel.

Introduction

Paclitaxel was first introduced into clinical practice as a treatment of recurrent ovarian cancer subsequent to platinum-containing chemotherapy. The combination of paclitaxel and cisplatin is the new treatment standard in first line ovarian cancer therapy.[1] In phase II single-agent trials, conducted in recurrent cisplatin refractory disease, various doses and schedules of administration have been proposed to test the safety and the activity of the drug.[2] In a randomized trial, no significant dose (135 versus 175 mg/m^2) or administration schedule (3 versus 24 h) dependency could be identified for clinical response.[3] Thus, the 3 h regimen, more attractive for out-patient delivery, has been approved as the recommended schedule. However, *in vitro* data have suggested schedule dependency for this agent, showing that prolonging drug exposure duration (more than 24 h) increased its cytotoxicity.[4] Clinical evaluation of protracted infusion has so far been limited to patients with breast cancer and lymphoma (96 h infusion), with some promising results in breast cancer patients.[5,6] Given this background, we decided to explore the tolerance and activity of a longer continuous infusion (7 days) paclitaxel schedule in ovarian cancer patients having failed paclitaxel given as 3 or 24 h i.v. administration.

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Patients and methods

Patient characteristics

Between February and September 1995, 13 women were enrolled the study. Patient characteristics are summarized in Table 1. All were heavily pretreated and had received at least one platinum-containing regimen and one paclitaxel-based chemotherapy protocol; the median number of prior chemotherapy lines was 5 (2–9), including 3 (1–4) platinum-based protocols. All patients were considered to have platinum-resistant tumors according to Markman's criteria[7] and had presented disease progression on paclitaxel given as a 3 or 24 h i.v. infusion. One had previously received both 1 h docetaxel (progression) and 24 h paclitaxel (stable disease). The patients' median performance status at inclusion was 2 (0–3) but all had normal hepatic and bone marrow function (ALT/AST < upper normal limit, absolute granulocyte count (AGC) > 1500 cells/mm^3, platelet count > 100 000 cells/mm^3).

Ten patients had measurable disease, mainly abdominal and/or pelvic recurrence, while three only had evaluable disease. The baseline median CA 125 blood level was 910 (136–108 530), reflecting a high tumor burden.

Table 1. Patient characteristics

Entered	13
Median age (range)	
Performance status	
0–1	6
2	3
3	4
Median number of prior therapy	5 (2–9)
Disease sites	
liver	1
abdomen/pelvis	13
lung/pleural	2
Prior paclitaxel treatment	
175/3 h	5
175/24 h	7
135/24 h	1

All patients gave their informed consent prior to study entry.

Drug administration

Paclitaxel were administered as a 168 h (7 day) continuous i.v. infusion, repeated every 3 weeks. Based on data from phase I studies of paclitaxel given over 96 h (4 days) and 120 h (5 days), a starting dose level/cycle of 105 mg/m^2 (15 mg/m^2/day × 7 days) was chosen. The daily dose was increased by 2.5 mg/m^2 increments, with at least three patients treated at each dose level until dose-limiting toxicity (DLT) occurred. If DLT of any type was seen during the first two treatment cycles in the first three patients, three further patients were to be accrued at that dose level. DLT was defined as (i) an absolute granulocyte count $< 0.5 \times 10^9$/l lasting 7 or more days or accompanied by the development of infection or fever requiring parenteral antibiotics, (ii) a platelet count <50 000 for ⩾7 days, (iii) grade 3 or greater non-hematological toxicity, with the exception of alopecia or emesis or (iv) dose reduction and/or treatment delay lasting longer than 1 week. No intrapatient dose escalation was allowed but dose reduction to the previous level was implemented for grade 4 for 7 days or more and/or febrile neutropenia toxicity.

Hematopoietic growth factors were not used nor was systematic premedication (steroids or anti-H1 or -2) given. Patients required a central venous device for all infusions. All cycles were administered in a in-patient setting, as ambulatory infusion pumps compatible with paclitaxel administration were not available at the time. The paclitaxel solution were prepared daily in glass solution containers. The 24 h paclitaxel calculated dose was diluted in 1000 ml of normal saline and infused through a tubing set with a non-PVC fluid pathway.

Patient monitoring

During therapy, complete blood counts were carried out at days 5 and 8 (the end of infusion), and every other day until hematological recovery; a clinical biochemistry profile (SMA 12) was obtained at days 5 and 8, and before the next cycle. CT scans were repeated after every two cycles, while serum CA 125 level was evaluated before each cycle.

Pharmacokinetics

Blood samples for paclitaxel assay were collected at 0, 48, 96, 144 and 178 h during the first cycle of therapy. Paclitaxel was measured by HPLC, as previously described.[8] The limit of quantification with this method was 5 nmol/l of plasma.

Response was evaluated following standard criteria (WHO scale), every two cycles. Survival and time to disease progression were measured from the date of entry in the study.

Results

Toxicity

The median number of cycles per patient was 3 (range 1–7). Four daily dose levels have been analyzed (15, 17.5, 20 and 22.5 mg/m^2). All patients and a total of 42 cycles were evaluable for toxicity. There were no cycle administration delays. DLT was hematological and was observed at dose level 4 (157 mg/m^2/cycle) (Table 2) with four episodes of grade 4 febrile neutropenia in three patients. Neutrophil nadir was often observed on day 8 (8–16) while recovery required a median of 7 days. One neutropenic patient died of acute *S. mitis*-associated sepsis (see below). Asymptomatic grade 3 thrombocytopenia was seen in two patients at level 4.

Three patients developed liver chemistry abnormalities during treatment: two patients (level 1 and 4) had minor AST/ALT elevation (2- to 3-fold) at the end of paclitaxel infusion; one had received a large amount of parenteral support, such as nutrition, antibiotics and anti-H2 during treatment. The third patient (level 4) initiated treatment despite poor performance status and obstructive syndrome; she developed an acute liver impairment profile during

Table 2. Hematological toxicity (WHO)

Dose level	Dose/cycle (mg/m^2)	Cycles given	Neutrophils			Platelets		
			Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
1	105	8	1	0	0	2	0	0
2	122.5	6	2	0	0	0	0	0
3	140	10	4/3	5/2	2/1	3/1	0	0
4	157.5	9	2/1	1/1	4/3[a]	1/1	2/2	0

[a]Four cycles in three patients.

Table 3. Pharmacokinetic data

Paclitaxel dose (mg/m^2)	Patient no.	Mean concentration (nM/l) (range)			
		H48	H96	H144	H168
105	3	16.9 (4.2–37.5)	45.2 (14.4–101)	43.8 (14–103)	53 (14.5–103)
122.5	3	24.4 (24.6–27)	31 (21–43)	38 (22–61)	27[a] (21–33)
140	3	21 (15–26)	24 (15–23)	30 (20–39)	54 (33–91)
157.5	3[b]	26 (18–46)	25 (18–39)	27 (22–29)	46 (25–67)

[a]Calculated from two patient samplings.
[b]Excluding a patient with intercurrent specticemia.

paclitaxel infusion, with high transaminases and LDH levels (respectively 20- and 10-fold) when treatment was stopped. Two days after, she had profound myelosuppression with grade 4 neutropenia and grade 3 thrombocytopenia; she died at day 10 from septic shock secondary to documented *S. mitis* septicemia. These three patients entered the study with normal liver function and two had no evidence of liver metastases.

Other toxicities were limited. Seven patients presented grade 1-2 asthenia. Two patients suffered from mucositis (one grade 1 and one grade 3), the more severe case being associated with grade 4 neutropenia. No peripheral neurotoxicity was observed, while residual cisplatin-related neurologic symptoms (grade 1-2) remained stable in two patients.

No patient experienced hypersensitivity reactions, although no premedication was given.

Activity

Of the 13 patients, 11 received at least two treatment cycles and were evaluable for activity. No objective response was seen, while three patients received five or six cycles with disease stabilization--all treated at level 3 (20 mg/m^2/day). Three of the 11 evaluable patients showed regression of their disease-related symptoms. A 50% decrease of CA 125 serum level was observed in two consecutive blood samples in five patients.

Pharmacokinetic data

Blood samples for paclitaxel measurements were available from all patients. There was a large intra-patient variability of paclitaxel levels (0-244%) at all points in the 7 day perfusion, with a consistent trend of an increased paclitaxel serum concentration at the end of the infusion. No clear relationship between paclitaxel dose and serum concentration could be established with a three patient sample for each dose level (Table 3).

Discussion

This phase I study, conducted in heavily pretreated patients, but with baseline hepatic and hematologic parameters within normal range limits has found that a daily paclitaxel dose of 22.5 mg/m^2/day given as a 7 days continuous i.v. infusion caused dose-limiting febrile neutropenia. Our recommended dose (RD)

with this schedule (140 mg/m^2/cycle) is similar to the RDs for the 4 or 5 day paclitaxel continuous infusion (140 and 150 mg/m^2, respectively).[5,9] Febrile neutropenia and mucositis were the limiting toxicities in both studies. We noted a total leucocyte count decrease from day 5, with the nadir often observed around day 8 (at the end of infusion or the day after) at the MTD level. The timing of this toxicity onset could limit the utility of prophylactic granulocyte colony stimulating factor as a means for further dose escalation.

No strong pharmacodynamic correlation could be found in this limited size, heavily pretreated population.

There were no objective responses. All patients had received extensive prior chemotherapy and this might be the principal explanation for this lack of activity. We found measurement of CA 125 levels to be of limited value in the corroboration of objective responses, as no tumor volume reduction was observed in patients with 'marker response' (two consecutive decreases greater than 50%). The poor reliability of CA 125 for monitoring response to paclitaxel has already been reported.[10]

Markman *et al.* have also explored the schedule dependency of paclitaxel in ovarian cancer patients during a phase II study of 96 h paclitaxel as salvage therapy in 3 or 24 h paclitaxel-resistant ovarian cancer patients.[11] Minimal clinical activity was found (no objective response in measurable disease) in their heavily pretreated population. Our results confirm their findings.

The schedule-dependant clinical resistance to paclitaxel has failed to show relevance in such a clinical setting (salvage treatment) for ovarian cancer, even if increased cytotoxicity has been demonstrated *in vitro* on human ovarian cell lines by prolonging exposure to paclitaxel.

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