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A dose escalation study of weekly docetaxel in patients with advanced solid tumors

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Abstract *Purpose*: To determine the maximum tolerated dose (MTD) and the dose-limiting toxicity (DLT) of weekly administration of docetaxel for three consecutive weeks every 4 weeks in patients with advanced solid tumors. *Patients and methods*: A total of 26 patients with malignant tumors refractory to conventional treatment were enrolled in this phase I study; their median age was 62 years. Of the 26 patients, 16 (62%) had previously received more than one chemotherapy regimen and 17 (65%) had previously received taxanes in a 3-week schedule. Docetaxel was administered after appropriate premedication at escalating doses (starting dose 30 mg/m^2) as a 1-h i.v. infusion for three consecutive weeks in cycles of 4 weeks. *Results*: A total of 68 chemotherapy cycles were administered with a median of three cycles per patient (range one to six). The DLT was reached at 45 mg/m^2 per week and the dose-limiting events were grade 4 neutropenia, febrile neutropenia, and treatment delay due to incomplete hematologic recovery. The MTD was defined at a dose of 42 mg/m^2/week. Grade 3/4 neutropenia occurred in seven patients (27%) (10% of cycles), and four patients (15%) developed febrile neutropenia. There were no deaths due to sepsis. Grade 2 peripheral neurotoxicity was observed in two patients (8%), grade 2 and 3 fatigue in 14 (54%), grade 2 edema in seven (27%), mild allergic reactions in two (8%) and lacrimation in three (12%). One (4%) complete response and eight (35%) partial responses (overall response rate 39%) were observed in 23 evaluable patients. Stable disease and progressive disease were observed in six patients (26%) and eight patients (35%), respectively. All responses were observed in patients with metastatic breast cancer, one of whom had progressed on paclitaxel-based and two of whom had progressed on docetaxel-based chemotherapy. *Conclusions*: The weekly administration of docetaxel for three consecutive weeks every 28 days is a feasible schedule with a favorable toxicity profile, and can be given on an outpatient basis. Moreover, this schedule of docetaxel administration seems to have an enhanced efficacy, especially in patients with advanced breast cancer who have failed front-line taxane-based chemotherapy.

Key words Docetaxel · Solid tumors

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Introduction

Docetaxel is a novel antimicrotubule agent which has demonstrated significant clinical activity in a wide range of solid tumors, including breast, lung, ovarian, head and neck, gastric and pancreatic cancer [1, 2, 3].

The optimal dose and schedule of administration of taxanes are important parameters and could modify their efficacy and toxicity profile [4]. Recent clinical studies have shown a lower incidence of toxic effects and particularly of hematologic toxicity with the weekly administration of taxanes as compared with their administration every 3 weeks [5, 6, 7]. In addition, the weekly administration schedule is anticipated to be more active because a higher number of dividing cells are exposed to the drug [8].

Thus, in a phase II study [5], the administration of paclitaxel at a dose of 175 mg/m^2 for six consecutive weeks of an 8-week cycle in chemotherapy-naive patients with advanced non-small-cell lung cancer resulted in an overall objective response rate of 56% and a 53% probability of 1-year survival. The toxicity of this regimen was acceptable, with grade 3/4 neutropenia occurring in 40% of the patients despite the markedly increased dose

intensity. In another phase I study [6] paclitaxel was given at escalating doses for 12 consecutive weeks achieving a dose intensity (90.75 mg/m^2 per week) which was twofold higher than that obtained with conventional (every 3-week) schedules. It is noteworthy that this schedule of paclitaxel administration did not show significant hematologic or nonhematologic toxicity. In addition, although all patients had been pretreated with paclitaxel and cisplatin, objective responses were documented in 4 of 13 patients (30%). Similarly, with a conventional administration schedule, docetaxel (100 mg/m^2 every 3 weeks) was complicated with grade 3/4 neutropenia, with or without fever, in 90% of the patients [1]. On the contrary, with a weekly administration schedule, docetaxel at doses of 20 to 52 mg/m^2 per week in 38 pretreated patients resulted in only five episodes of grade 3 leukopenia corresponding to 14% of patients, whilst no grade 4 leukopenia occurred [7]. In this study, docetaxel was administered weekly for six consecutive weeks, followed by 2 weeks of rest and the dose-limiting toxicities (DLTs) were fatigue and asthenia. In another phase I/II study of weekly docetaxel in pretreated patients with metastatic breast cancer, the recommended dose for the phase II study was 35 mg/m^2. In this latter study, the objective response rate was 50% with 0% incidence of febrile neutropenia [9].

In a more recent phase II study, the weekly administration of docetaxel at 40 mg/m^2 for six consecutive weeks and then 2 weeks of rest in patients with metastatic breast cancer was associated with a 41% overall response rate and no grade 4 toxicity occurred [10]. The most common cumulative toxicities were fatigue, fluid retention and eye tearing/conjunctivitis. A similar cumulative toxicity was observed in another phase I study [11].

Weekly administration of taxanes has revealed that the DLTs are different from those observed with 3-week schedules, i.e. fatigue and peripheral neuropathy versus neutropenia and febrile neutropenia, respectively [7, 8]. Since the weekly schedules allow dose intensification, and in some tumors dose intensification may be associated with an increased efficacy, it is reasonable to evaluate this schedule in more detail.

Based on these considerations, we conducted a phase I study in order to determine the DLT and the maximum tolerated dose (MTD) of docetaxel given weekly as a 1-h infusion for three consecutive weeks every 4 weeks in patients with advanced solid tumors refractory to standard treatment.

Patients and methods

Patients

Patients with histologically or cytologically confirmed solid tumors refractory to standard treatment and documented disease progression were enrolled into the study. Inclusion criteria were: a WHO performance status ≤2; age ≤75 years; life expectancy at least 3 months; adequate renal (serum creatinine concentration ≤2 mg/dl), liver (total bilirubin level ≤1.5 mg/dl, transaminases less than 1.5 times the upper limit of normal or less than three times if hepatic metastases were present and alkaline phosphatase less than 2.5 times the upper limit of normal) and bone marrow (neutrophils ≥1500/dl and platelets ≥100,000/dl) function. In addition, patients had to have stopped prior chemotherapy or radiation therapy for a minimum of 4 weeks before entering the study. Bidimensionally measurable disease was not mandatory for study enrollment. Patients with pre-existing motor or sensory neurotoxicity of grade 2 or more or congestive heart failure or unstable angina pectoris were not eligible. Patients with malnutrition (loss of more than 20% of body weight), active infection as well as brain metastases which failed to improve with radiotherapy or patients with symptomatic brain metastases were also not eligible. The study was approved by the Ethical and Scientific Committees of our hospital and all patients gave written informed consent to participate in the study.

Treatment

Docetaxel was administered at escalating doses (starting dose 30 mg/m^2 per week) as a 1-h i.v. infusion for three consecutive weeks every 4 weeks. All patients received standard premedication with methyl prednisolone (16 mg orally twice daily for 2 days starting 12 h before docetaxel administration), and diphenhydramine and cimetidine (50 mg and 400 mg, respectively) 30 min before the administration of docetaxel. A starting dose of docetaxel of 30 mg/m^2 per week was chosen because in our previous phase I/II study of weekly docetaxel and concomitant radiotherapy in non-small-cell lung cancer patients the MTD was 30 mg/m^2 per week [12].

The dose levels 30, 35, 40, 42 and 45 mg/m^2 per week were evaluated. No intrapatient dose escalation or growth factor support was allowed. The treatment was postponed if the absolute neutrophil count was <1000/dl and/or platelets <75,000/dl on the day of docetaxel administration (days 8 and 15). Toxicities were evaluated at the first chemotherapy cycle and DLT events were defined as follows: grade 4 neutropenia and/or thrombocytopenia lasting for more than 2 days, febrile neutropenia (>38.5 °C) for more than 48 h, any grade 3 or more nonhematologic toxicity except for alopecia and nausea/vomiting and any treatment delay on days 8 and 15 due to unresolved toxicity.

Three patients were enrolled at each dose level. If DLT occurred in one of the three patients, three additional patients were enrolled at that dose level. The MTD was defined as the next lower dose level at which at least two out of three or three out of six patients presented DLT events. In the case of DLT, the treatment was resumed after the resolution of toxicity and at the previous lower dose level.

Patient evaluation

Baseline evaluations included patient history, physical examination, chest radiographs, full blood count (FBC) with differential and platelet count, blood chemistry, electrocardiography (ECG), computed tomography (CT) scans of the chest, abdomen and pelvis, while whole-brain CT scans were performed when clinically indicated. FBCs with differential and platelet count, whole blood chemistry and clinical examination were performed weekly before each treatment. In patients with grade 4 myelosuppression FBCs with differential and platelet count were performed daily until hematologic recovery. Toxicities were recorded according to the WHO criteria [13].

Responses to treatment were evaluated according to the WHO criteria [13] in patients with bidimensionally measurable disease after each cycle by physical examination or chest radiographs if appropriate. In all other patients response to treatment was evaluated by imaging studies every two chemotherapy cycles.

Results

A total of 26 patients were enrolled in the study. All patients were assessable for toxicity and 23 of them for

response to treatment. Three patients were not evaluable for response because they did not have bidimensionally measurable disease. Patient characteristics are presented in Table 1. The median age was 62 years and 23 patients (89%) had a performance status 0–1. Of the 26 patients, 16 (62%) had previously received more than one chemotherapy regimen and 17 patients (65%) had previously received taxanes on a 3-week schedule.

A total of 68 chemotherapy courses of docetaxel were delivered. The median number of courses was three per patient (range one to six). The DLT was reached at dose level V (45 mg/m^2; Table 2) at which five out of six patients developed DLT events: grade 4 neutropenia (two patients), treatment delay due to incomplete hematologic recovery (two patients) and febrile neutropenia (one patient). Therefore, the MTD which is the dose recommended for further phase II studies is 42 mg/m^2 per week. At dose level IV (42 mg/m^2) two patients required delay of their treatment because of incomplete recovery from hematologic toxicity.

Table 1 Patient characteristics

Patients enrolled	26
Age (years)	
Median	62
Range	43–74
Sex (male/female)	2/24
Performance status (WHO)	
0	9 (35%)
1	14 (54%)
2	3 (11%)
Primary tumor site	
Breast	19 (73%)
Ovarian	3 (11%)
Prostate	1 (4%)
Endometrial	1 (4%)
Penis	1 (4%)
NHL	1 (4%)
No. of prior regimens	
1	10
2	8
3	8
Prior taxane-based chemotherapy	
Docetaxel	10 (38%)
Paclitaxel	5 (19%)
Docetaxel + paclitaxel	2 (8%)

The median delivered dose intensity was 21 mg/m^2 per week (91% of the protocol planned dose) at dose level I, 25 mg/m^2 per week (96%) at dose level II, 28 mg/m^2 per week (94%) at dose level III, 30 mg/m^2 per week (95%) at dose level IV and 27 mg/m^2 per week (78%) at dose level V (the last dose level) which was the lowest as a percentage of the protocol planned dose among the five dose levels and was due to treatment delays because of hematologic toxicity.

Hematologic toxicity was mild (Table 3). Grade 3 and 4 neutropenia was observed in three and four patients, respectively, corresponding to 10% of the chemotherapy cycles. In addition, febrile neutropenia occurred in four patients (15%) and all patients required hospitalization for i.v. antibiotics. There were no deaths due to sepsis. No patient developed grade 4 anemia or thrombocytopenia (Table 3).

Nonhematologic toxicity was also mild. Grade 3 or 4 toxicity was rarely seen (Table 4). Grade 3 and 4 diarrhea was observed in one patient each, respectively, whilst grade 3 mucositis also occurred in one patient. Grade 2 peripheral neurotoxicity was observed in two patients at dose level V. Both patients had previously been treated with regimens containing taxanes and vinca alkaloids. In contrast, fatigue was a very common toxicity at all dose levels: grade 2 and 3 fatigue was observed in 12 patients (46%) and two patients (8%), respectively. However, six patients with fatigue also suffered from grade 2 anemia (five patients) or grade 3 anemia (one patient). This suggests a possible correlation between these toxicities. Edema was relatively frequent and seems to have been related to the cumulative dose: grade 2 edema was observed in eight patients (32%) of whom three had already been treated with docetaxel (mean cumulative dose 600 mg/m^2). Mild hypersensitivity reactions occurred in two patients while three patients developed lacrimation and three patients had nail changes.

Although the objective of the study was not the efficacy of the treatment, responses were observed at all dose levels. One patient (4%) achieved a complete response and eight patients (35%) a partial response. In addition six patients (26%) had stable disease and eight (35%) progressive disease. All patients with objective response (two at level I, one at level II, three at level IV

Table 2 Dose-limiting events (DLT) per dose level by the first cycle

Level	Docetaxel (mg/m^2)	No. of patients[a]	No. of patients with DLT	DLT		
				Event	Grade	No. of patients
I	30	5 (3)[a]	1	Diarrhea	3	1
II	35	5 (2)	1	Asthenia	3	1
III	40	4 (2)	–	–		
IV	42	6 (1)	1	Neutropenia	4	1
V	45	6 (2)	5	Neutropenia	4	2
				Febrile neutropenia	3	1
				Treatment delay		2

[a] Numbers in parentheses indicate the number of patients who had received two or more prior chemotherapy regimens

Table 3 Hematologic toxicity (in all cycles) and all patients. The numbers of patients with each toxicity are shown

Level	No. of patients	Anemia (grade)			Neutropenia (grade)			Thrombocytopenia (grade)			Febrile neutropenia
		2	3	4	2	3	4	2	3	4	
I	5	–	–	–	–	–	–	–	–	–	–
II	5	3	–	–	1	–	–	–	–	–	–
III	4	–	–	–	–	–	–	–	–	–	–
IV	6	–	1	–	2	1	1	–	1	–	2
V	6	2	1	–	1	2	3	3	1	–	2
Total	26	5	2	–	4	3	4	3	2	–	4

Table 4 Nonhematologic toxicity by dose level. The results are expressed in terms of treated patients per dose level

	Level I Grade			Level II Grade			Level III Grade			Level IV Grade			Level V Grade		
	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4
Nausea/vomiting	–	–	–	–	–	–	–	–	–	1	–	–	–	–	–
Diarrhea	–	1		–	–	–	–	–	–	1	–	–	1	–	1
Mucositis	–	–	–	–	–	–	–	1	–	–	–	–	1	–	–
Neurotoxicity	–	–	–	–	–	–	–	–	–	–	–	–	2	–	–
Fatigue/asthenia	4	–	–	1	2	–	3	–	–	1	–	–	3	–	–
Edema	1	–	–	2	–	–	2	–	–	1	–	–	2	–	–
Hypersensitivity reactions	–	–	–	1	–	–	1	–	–	–	–	–	–	–	–
Lacrimation	–	–	–	–	–	–	1	–	–	1	–	–	1	–	–
Nail changes	–	–	–	–	–	–	–	–	–	1	–	–	2	–	–

and three at level V) suffered from metastatic breast cancer, and one of these patients had progressed on paclitaxel-based chemotherapy and two others on docetaxel-based chemotherapy. The duration of responses ranged from 1 to 5 months.

Among 17 patients who had previously received taxane-based treatment, four responded with a median time to disease progression of more than 6 months.

Discussion

The results of this study clearly indicate that docetaxel can be administered on a weekly basis for three consecutive weeks in cycles of 4 weeks without growth factor support. This schedule of docetaxel is well tolerated and the MTD, which is the dose recommended for further phase II studies, is 42 mg/m^2 per week. In addition, our data confirm the results of previous studies indicating that the weekly administration of docetaxel is associated with significantly less myelosuppression than the conventional 3-week schedule [7]. Indeed, up to 70% of patients treated with docetaxel at a dose of 100 mg/m^2 every 3 weeks develop grade 3 and 4 neutropenia. Conversely, only seven patients (27%) developed grade 3 or 4 neutropenia with the weekly schedule in the present study, despite the fact that the patients were heavily pretreated. It should be noted that the MTD of the weekly docetaxel administration (42 mg/m^2 per week) allows dose intensification, compared with the 3-week schedule. Anemia and thrombocytopenia were very rare. A similar lack of myelosuppression has also been observed with the weekly administration of paclitaxel [6].

Nonhematologic toxicity was also very mild. Asthenia was the main complaint of the patients irrespective of the dose level. Grade 2 asthenia occurred in 14 patients, and two patients at dose level II reported grade 3 asthenia after the administration of repeated chemotherapy cycles, suggesting that this toxicity may be cumulative. Grade 2 sensory neurotoxicity was observed in two patients at dose level V. Nevertheless, fatigue and peripheral neuropathy were not the DLT events as has already been reported with paclitaxel and docetaxel in other studies [5, 7]. The low incidence of neurotoxicity should be interpreted with caution since the median number of administered courses was three per patient. It is well known that neuropathy is a cumulative toxicity when docetaxel is administered every 3 weeks [3]. Finally, a moderate fluid retention syndrome was observed in eight patients (30%).

The efficacy of the weekly administration schedule of docetaxel remains an open question. Despite the fact that the majority of breast cancer patients enrolled in the present study had already received both taxanes and anthracyclines, and probably had chemoresistant tumors, one complete and eight partial responses were observed in patients with metastatic breast cancer. It is important to note that one of these patients had paclitaxel-refractory disease whilst two others had received docetaxel in combination with anthracyclines at least within the last 6 months before the administration of weekly docetaxel. Therefore, it is reasonable to hypothesize that, in some breast cancer patients, the weekly administration of docetaxel may overcome the drug resistance observed with the 3-week schedule. A similar phenomenon has also been observed with paclitaxel given on a weekly basis [5, 6]. Furthermore, in a phase I

study in pretreated metastatic breast cancer patients, the weekly administration of docetaxel was associated with an objective response in 10 out 14 taxane-naive patients and in three out five paclitaxel-pretreated patients [14].

In conclusion, the weekly administration of docetaxel for three consecutive weeks in cycles of 4 weeks is a feasible outpatient schedule with a favorable toxicity profile. In addition, this schedule showed an enhanced efficacy in heavily pretreated breast cancer patients. The recommended dose for future phase II studies is 42 mg/m^2 per week. Further studies are needed to evaluate its combination with other active drugs.

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