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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/m²) 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/m² 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/m²/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

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/m² for six consecutive weeks of an 8-week cycle in chemotherapy-naïve 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/m² 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/m² 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/m² 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/m². 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/m² 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.

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**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/m² 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/m² 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/m² per week [12].

The dose levels 30, 35, 40, 42 and 45 mg/m² 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 of three or four 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