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SHORT COMMUNICATIONS

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Risk of severe acute hypersensitivity reactions after rapid paclitaxel infusion of less than 1-h duration

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Abstract On the basis of the safety of the 1-h paclitaxel infusion schedule in prior studies we attempted to evaluate the feasibility of a shorter infusion schedule (< 1-h), given the general lack of published data or of attempts at applying this strategy. Before receiving paclitaxel, all patients were premedicated with promethazine, dexamethasone, and ranitidine; they were then given paclitaxel at a dose of 175 mg/m^2 diluted in 150 ml normal saline. Four patients were evaluated, two with breast cancer, one with ovarian carcinoma, and one with non-small-cell lung cancer. All had received at least two prior cycles of paclitaxel and had never exhibited any hypersensitivity reaction. In all four patients, adverse signs and symptoms were observed at 5–15 min after the start of paclitaxel administration. These included generalized erythema (three patients), angioedema (all patients), sinus tachycardia (all patients), dyspnea (all patients), and increased sweating (all patients). One patient experienced acute diarrhea. Significant changes in vital signs were recorded in all patients, but there was no dysrhythmia or syncope. Thereafter, drug infusion was interrupted and supportive measures were initiated with dimethidene maleate, ranitidine, and methylprednisolone. In all patients, symptoms resolved over the next 15–30 min, and paclitaxel was reinstituted at the standard 1-h rate with no further sequelae. Paclitaxel administration in < 1 h did not prove to be safe in the current pilot experience and, therefore, cannot be recommended.

Key words Paclitaxel · 1-h infusion · Solid tumors · Outpatient setting

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Introduction

On the basis of the safety of the 1-h paclitaxel infusion protocol in our prior study [1] we decided to evaluate the feasibility and safety of shorter infusion schedules.

Because of severe hypersensitivity reactions seen in the phase I evaluation of paclitaxel, treatment programs were developed for administration of the drug over 24 h with antiallergic premedication, and their safety remained unknown. Further studies established the safety of shorter (3-h) infusion schedules with premedication (steriods, antihistamines, and H2-blockers). More recently, we and other investigators [1, 2] have demonstrated that paclitaxel can be given equally safely over a 1-h period with premedication (steriods, antihistamines, and H2-blockers) being given just 1 h before initiation of the paclitaxel infusion rather than on the standard premedication protocols, which include the administration of steroids at 12 and 6 h before the triple (steroid, antihistamine, and H2-blocker) or single dose of promethazine, ranitidine, and dexamethasone is given immediately before paclitaxel. Therefore, the safety of the 1-h paclitaxel infusion given within 1 h of premedication made the drug very easy to give in the outpatient setting, allowing its incorporation into complex multidrug chemotherapy regimens such as the combination of paclitaxel, ifosfamide, and cisplatin [3]. However, to our knowledge, data do not exist concerning the safety of paclitaxel administration in less than 1 h. For that reason we attempted to give paclitaxel in an infusion of < 1-h duration.

Patients and Methods

Patients

Four patients with histologically confirmed malignancy who were eligible to receive chemotherapy with single-agent paclitaxel were evaluated in this pilot study (Table 1). Two patients had metastatic breast cancer, one had non-small-cell lung cancer, and one had

Table 1 Patients' characteristics and side effects of rapid paclitaxel infusion (*BP* Systolic blood pressure, *NSCLC* non-small-cell lung cancer)

Patient number	Disease type	Target infusion time of paclitaxel (min)	Side effects
1	Breast cancer	30	Generalized erythema, angioedema, sinus tachycardia (120/min), BP drop (60 mmHg), dyspnea, increased sweating
2	Breast cancer	30	Angioedema, sinus tachycardia (120/min), BP drop (70 mmHg), dyspnea, increased sweating
3	NSCLC	45	Generalized erythema, diarrhea, angioedema, sinus tachycardia (130/min), BP drop (70 mmHg), dyspnea, increased sweating
4	Ovarian cancer	45	Generalized erythema, angioedema, sinus tachycardia (140/min), BP drop (80 mmHg), dyspnea, increased sweating

ovarian cancer. All patients had previously received at least two cycles of single-agent paclitaxel infused over 1 h and had never exhibited any hypersensitivity reaction. The dose of paclitaxel given to all four patients was 175 mg/m^2.

Schedule of paclitaxel administration

Before receiving paclitaxel, all patients were premedicated with 1 ampule (50 mg) of promethazine given i.m. followed by 16 mg dexamethasone given i.v. in 250 ml normal saline as a 20-min infusion and then 50 mg ranitidine given i.v. in 250 ml normal saline as a 20-min infusion. Paclitaxel was diluted in 150 ml normal saline in standard glass bottles with in-line filtration and tubing as supplied by the manufacturer and was infused through a large peripheral vein or dual-lumen central Hickmann catheter. To accelerate the infusion rate, which is limited by the vacuum in the glass bottle, we introduced air via a 20-ml sterile plastic syringe (six to seven times) to increase the pressure in the bottle. Thereafter, the infusion rate was regulated by an external volumetric pump such that drug administration was completed at 30–45 min.

Monitoring during rapid paclitaxel infusion

Before the start of the brief ($<$1-h) paclitaxel infusion, patients were examined clinically by one of the investigators; their pulse rate, blood pressure, and respiration rate were recorded by a senior nurse and a baseline electrocardiogram (ECG) was obtained. Vital signs were recorded every 5 min after initiation of the paclitaxel infusion, and a second ECG was obtained at 15 min thereafter, or earlier if clinically indicated.

Results and discussion

In all four patients, symptoms and signs of adverse reactions were observed at 5–15 min after the start of the paclitaxel infusion ($<$1 h). These included generalized erythema (three patients), angioedema (all patients), sinus tachycardia, dyspnea, and increased sweating (all patients). One patient experienced three episodes of acute diarrhea. The systolic blood pressure dropped to 60, 70, 70, and 80 mmHg and the pulse rate increased to 120, 120, 130, and 140 beats/min,respectively (also see Table 1). Soon after these signs were encountered the drug infusion was interrupted and supportive measures were undertaken. Dimethidene maleate at 4 mg and methylprednisolone at 40 mg were given by slow i.v. infusion and a normal saline solution was started. In all patients, symptoms resolved over the next 15–30 min and paclitaxel was subsequently infused at the standard 1-h rate. None of our patients experienced any other hypersensitivity reaction, and paclitaxel infusion as well as their planned chemotherapy cycle was completed without other adverse events. For these reasons the present study closed very early.

Therefore, this preliminary pilot experience in attempting to give paclitaxel by infusion of $<$1-h duration indicates that such a strategy is harmful and that current preventive measures (antiallergic premedication) do not provide adequate safety. Many investigators are presently evaluating weekly lower doses of paclitaxel (60–100 mg/m^2) given over 1 h in various solid tumors [4–6]. It is possible that at these lower than conventional (every 3 weeks) single doses a rapid, e.g., 30-min, infusion protocol might be feasible and provide convenience when, for instance, paclitaxel is used as a radiosensitizer given concurrently with external radiation [6].

It is anticipated that the 1-h infusion schedule of paclitaxel would provide adequate safety and offer the ability to introduce paclitaxel in complex multidrug chemotherapy regimens in a total outpatient program. One of the reasons that prompted us to give paclitaxel on shorter schedules stems from an effort to simplify complex multidrug regimens, including lengthy pre- and posthydration protocols, for the convenience of both the patient and the nursing staff in the outpatient department.

Moreover, it is not known whether more prolonged premedication protocols as carried out by most investigators, who give additional dexamethasone at 12 and 6 h before paclitaxel administration, would have prevented the above-mentioned hypersensitivity reactions. In this context, administration of paclitaxel in 1 h is considered largely unsafe and cannot currently be recommended for further testing.

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