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Clinical Oncology Update

The Clinical Development of Paclitaxel and the Paclitaxel/Carboplatin Combination

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Paclitaxel and carboplatin have nonoverlapping toxicities with a broad range of clinical activity. The combination of escalating dose paclitaxel and carboplatin dosed to a fixed area under the curve (AUC) was explored in a series of phase I studies. 76 patients were treated with paclitaxel over three hours followed by a 30 min carboplatin infusion, dosed by the Calvert formula to a target AUC of 4.0 or 4.5 mg/min/ml^{-1}. The maximum tolerated dose of paclitaxel was 270 to 290 mg/m^2, with a dose limiting toxicity of peripheral sensory neuropathy. Activity was seen in lung cancer, with a paclitaxel dose at or above 230 mg/m^2. Neuropathy correlated with paclitaxel AUC due to nonlinear pharmacokinetics at higher doses. Ongoing studies include the use of amifostine as a neuroprotectant and phase II studies of the paclitaxel/carboplatin regimen in head and neck cancer, small cell lung cancer and sarcomas. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

PACLITAXEL IS a member of a class of new chemotherapy agents which act via a novel mechanism and has activity against a broad range of solid tumours. For these reasons, paclitaxel has been applied to the treatment of a variety of advanced malignancies. It is currently approved in the U.S.A. for use in treatment of patients with refractory ovarian and breast cancer. The current challenges in the development of paclitaxel include determination of the optimal dose and schedule for its use, how to use paclitaxel in combination with other antineoplastic agents and how to use paclitaxel effectively in the initial therapy of cancer.

HISTORY

Paclitaxel was discovered as part of a National Cancer Institute (NCI)-sponsored drug screen. In the 1960s, a crude extract of the bark of the Western yew, *Taxus brevifolia*, was isolated and found by Wall and Wani to have cytotoxic activity against a number of murine tumours. They identified paclitaxel as the active agent in 1971 and described its structure [1]. Development of paclitaxel lagged owing to difficulty in isolating and preparing the active drug. However, in 1979, the unique mechanism of paclitaxel was identified [2, 3] and interest in its clinical development intensified. Phase I clinical trials began in 1983. Hypersensitivity reactions were identified as a major obstacle and the NCI mandated a premedication regimen and a 24 h infusion schedule. A number of trials demonstrated the activity of paclitaxel in cisplatin-refractory ovarian cancer [4–9] and paclitaxel was approved by the FDA for this indication in December 1992.

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CLINICAL PHARMACOLOGY

Microtubules are formed through polymerisation of tubulin and function in maintaining the mitotic spindle apparatus, as well as sustaining motility, anchorage, shape and intracellular transport [10]. Paclitaxel binds to a site on the beta-subunit of tubulin which is distinct from the binding site of the vinca alkaloids. Horwitz and Schiff discovered that paclitaxel shifts the dynamic equilibrium of tubulin assembly/disassembly toward assembly [11]. Microtubules formed in the presence of paclitaxel are unable to undergo physiological reorganisation and vital mitotic and interphase processes are disrupted. Morphological abnormalities can be found in

affected microtubules [12, 13] and cells become arrested at the G_2/M interphase of the cell cycle. G_2 arrest may sensitise paclitaxel-exposed cells to the lethal effects of radiotherapy [14].

Two mechanisms of paclitaxel resistance have been noted *in vitro*. Paclitaxel-resistant Chinese hamster ovary cells express altered alpha- and beta-tubulin [15, 16] with impaired microtubular polymerisation. Continuous exposure to paclitaxel is necessary in order to allow microtubular assembly to proceed normally. A second mechanism of drug resistance is through expression of membrane P-glycoprotein, a multidrug resistance efflux pump [17–19]. Paclitaxel is a substrate for this pump, as are vinca alkaloids, anthracyclines and etoposide.

The pharmacology of paclitaxel is linear with prolonged infusion schedules, but appears to be nonlinear with shorter infusions [20–22]. Biologically active drug concentrations can be achieved with a variety of infusion schedules. Paclitaxel binds extensively to plasma proteins and has a large volume of distribution. Biliary excretion and extensive tissue binding are responsible for most of the clearance of paclitaxel [23, 24]; renal clearance is responsible for less than 5% of systemic clearance and, therefore, dosing is not affected by renal function [25, 26]. The primary biliary metabolite is a hydroxylated paclitaxel formed by the CYP2C and CYP3A isoforms of cytochrome P450. Dose modification appears to be necessary in patients with impaired hepatic function [23, 26].

Paclitaxel interacts with other antineoplastic agents when given in combination. In one phase I study [27], patients were given the combination of paclitaxel and cisplatin in alternating sequence. Paclitaxel clearance was reduced by one-third when paclitaxel was given following cisplatin, resulting in significantly greater neutropenia. As a result, paclitaxel is now given prior to cisplatin. Paclitaxel can be given concurrently with or following doxorubicin. However, administration of paclitaxel prior to doxorubicin leads to a 70% decline in the clearance of doxorubicin, with significant resulting myelosuppression and cardiac toxicity [28]. There is also an increased degree of haematological toxicity when paclitaxel is given prior to cyclophosphamide, but there is no evidence that the pharmacokinetics of either drug are altered when they are given in combination [29]. Similar interactions may exist for other agents when given in combination with paclitaxel.

TOXICITIES

Neutropenia and neurological toxicity are the common dose-limiting toxicities encountered in phase I trials of paclitaxel. However, hypersensitivity reactions were the most significant problems during the early development of paclitaxel. Hypersensitivity reactions usually occur within minutes of beginning the drug infusion and bronchospasm, hypotension, urticaria, extremity pain, diaphoresis, flushing and angiooedema can be seen. 1 patient in an early trial died from anaphylaxis. This reaction has been linked to histamine release precipitated by the Cremophor EL vehicle [30]. The early phase studies were completed under a 24 h infusion schedule, with prophylactic premedication with steroids and histamine blockers. The incidence of hypersensitivity reactions is now in the 1–3% range [31] and the premedication schema has allowed the development of shorter infusion schedules.

Neutropenia is the primary dose-limiting toxicity of paclitaxel. The maximum tolerated dose (MTD) of paclitaxel given without haematopoietical growth factors on a 24 h schedule is 175–200 mg/m^2. Neutropenia with subsequent doses is not cumulative. Thrombocytopenia and anaemia are usually not clinically significant. The most important pharmacological parameter relating to neutropenia is the duration of plasma drug levels greater than 0.05–0.1 μM [21, 32].

Paclitaxel causes a peripheral sensory neuropathy similar to that seen with vinca alkaloids. Motor and autonomic disorders can also occur, particularly in the presence of preexisting neuropathic processes. Although severe neurotoxicity is not common at doses less than 200 mg/m^2, it generally precludes dose escalation significantly above a dose of 250 mg/m^2. It has been proposed that the mean paclitaxel area under the curve (AUC) can predict for neurological or musculoskeletal toxicity [22].

CURRENT USE

Paclitaxel is currently in use as a standard frontline agent in the treatment of advanced ovarian cancer. It is currently undergoing evaluation as part of a sequential adjuvant chemotherapy regimen in women with node positive breast cancer. Paclitaxel is a component of regimens in widespread use against advanced small cell and non small cell lung cancer (NSCLC), head and neck cancer, breast cancer, oesophagus cancer, bladder cancer and cancer of unknown primary.

PHASE I STUDIES OF PACLITAXEL AND CARBOPLATIN AT ROSWELL PARK CANCER INSTITUTE

Using paclitaxel and carboplatin in combination is reasonable, as these two agents have substantial clinical activity in a range of malignancies, as well as nonoverlapping toxicities. There appears to be little pharmacokinetic interaction when paclitaxel is given first. Carboplatin has no effect on the disposition or elimination of paclitaxel and the observed carboplatin AUC is not significantly different from the target AUC when carboplatin is given following paclitaxel [33].

A series of phase I studies were carried out under the direction of Patrick Creaven at the Roswell Park Cancer Institute. Patients were treated with escalating doses of paclitaxel and a fixed target AUC of carboplatin. The target AUC was set relatively low, to allow for aggressive dose escalation of the paclitaxel. Patients who received surgery, radiotherapy, or chemotherapy within 3 weeks of enrolment were excluded, as were patients with active uncontrolled infection, congestive heart failure or arrhythmia, pregnancy or lactation, prior paclitaxel or carboplatin, neurological compromise, diabetes, or inadequate hepatic, renal, or haematological parameters at enrolment. Patients received paclitaxel as a 3 h infusion, followed by a 30 min infusion of carboplatin dosed by the Calvert formula [34] to a target AUC. The standard premedication regimen including dexamethasone, cimetidine and diphenhydramine was given in all trials and courses were repeated at 4 week intervals.

A total of 76 patients, 45 men and 31 women, with a median age of 54 years (range 27–72) were treated on the three phase I trials. 16 had an ECOG performance status of 0, 44 had a performance status of 1 and 16 had a performance status of 2. 30 patients had a diagnosis of NSCLC. 9 patients had an unknown primary, 7 had squamous cell carcinoma of the head and neck, and 5 had mesothelioma. 34 had not previously been treated with chemotherapy, 33 had received one prior chemotherapy regimen, 8 had received two prior regimens, and 1 patient had received three prior chemotherapy regimens.

The objective of the first study was to define the MTD and dose-limiting toxicities (DLTs) of the combination of

paclitaxel and carboplatin without cytokine support in patients who had received prior chemotherapy. Carboplatin was dosed at a target AUC of 4.0 mg/min/ml^{-1} in this study. 10 patients received paclitaxel at doses of 100 and 135 mg/m^2. Myelosuppression was the DLT of this regimen with a MTD of 135 mg/m^2. Study II continued the dose escalation of paclitaxel with G-CSF support, with the same target AUC of carboplatin in previously treated patients. 32 additional patients were entered at doses ranging from 135 to 290 mg/m^2. The DLT of paclitaxel given with a fixed dose of carboplatin and cytokine support is a grade 3 sensory neuropathy seen at a dose of 290 mg/m^2 and the MTD was defined at 290 mg/m^2. Mild reversible myalgias and arthralgias were also seen at 290 mg/m^2, but the extent and severity of granulocytopenia and thrombocytopenia was not severe. The pattern of toxicity recorded at each dose level is listed in Table 1. Five responses were seen in patients treated in this phase of the study. 2 patients with squamous cell carcinoma of the head and neck treated at a dose of 205 mg/m^2 each had a partial response 5 months in duration. 2 patients with non small cell lung cancer had a partial response; one treated at 230 mg/m^2 had a response lasting 3 months and the other treated at 270 mg/m^2 had a response lasting 9 months. A patient with metastatic colorectal cancer had a response of 2 months duration after receiving paclitaxel at 250 mg/m^2.

Previously untreated patients with advanced cancer were treated in study III with carboplatin dosed to a target AUC of 4.5 mg/min/ml^{-1} and paclitaxel, starting at a dose of 135 mg/m^2. Patients in this study did not receive cytokine support. 30 patients were treated at doses ranging from 135–290 mg/m^2. Although grade 4 granulocytopenia was seen in all patients treated above 250 mg/m^2, it did not persist longer than 5 days. Sensory neuropathy was the DLT at 290 mg/m^2 and the MTD was 270 mg/m^2. The toxicities seen at each dose level are recorded in Table 2. Three responses were seen within this trial. 1 patient with a carcinoma of unknown primary had a partial response lasting 3 months at a dose of 205 mg/m^2 of paclitaxel. Two partial responses were observed in patients with NSCLC, one of 4 months duration at a dose of 270 mg/m^2 and one of 3 months duration at a dose of 290 mg/m^2.

30 patients with NSCLC cancer were treated on these three trials. 18 had not received prior chemotherapy, 10 had received one prior chemotherapy regimen and 2 had received two prior regimens. 6 had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 17 had a performance status of 1, and 7 had a performance status of 2. 16 patients had locally advanced disease and 14 had metastatic disease. 30 patients were evaluable for toxicity, and 25 were evaluable for response. 9 patients were treated at a dose of paclitaxel less than 230 mg/m^2. None of these patients had a response. 4 of 16 patients treated with 230 mg/m^2 or greater of paclitaxel had a partial response. These results suggest a dose–response relationship for paclitaxel in NSCLC.

Carboplatin and paclitaxel pharmacokinetics were measured in these studies. Paclitaxel was measured by a modification of the reverse phase HPLC method of Jamis-Dow [35]. Pooled pharmacokinetic parameters from 35 patients treated at each paclitaxel dose level are listed in Table 3. Paclitaxel has linear pharmacokinetics at doses from 100 to 250 mg/m^2, with a constant clearance of 21–28 l/h. In this same dose range, the measured AUC increases in proportion to the administered dose, from 8 μg/ml/h^{-1} at 100 mg/m^2 to 21.9 μg/ml/h^{-1} at 250 mg/m^2. At doses of 270 mg/m^2 and greater, the clearance of paclitaxel is saturated and falls below 20 l/h, while the measured AUC of the drug escalates rapidly to over 40 μg/ml/h^{-1} at 290 mg/m^2 of paclitaxel. Carboplatin AUC was measured as non-protein bound platinum by atomic absorption spectroscopy in 14 patients treated on studies I and II, and in 9 patients treated on study III. The measured carboplatin AUC was 4.6 mg/ml/min^{-1} in the 14

Table 1. *Toxicities in study II—by dose level*

	Paclitaxel dose (mg/m^2)																											
	135 (n=4)				175 (n=3)				205 (n=6)				230 (n=7)				250 (n=3)				270 (n=3)				290 (n=6)			
Grade	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV
Leucopenia	–	–	–	–	1	–	–	–	2	1	2	–	2	–	–	1	–	–	–	–	1	1	–	–	1	2	1	–
Granulocytopenia	–	–	–	–	–	–	–	–	–	1	–	1	–	–	–	1	–	–	–	–	–	–	–	–	–	1	–	1
Thrombocytopenia	–	–	–	–	2	–	–	–	5	–	–	–	1	–	–	1	–	–	–	–	1	–	–	–	6	–	–	–
Nausea/vomiting	3	–	–	–	2	–	–	–	–	–	1	–	3	–	1	–	2	–	1	–	–	–	–	–	1	–	–	–
Arthralgia	2	–	–	–	2	–	–	–	2	2	–	–	1	1	–	–	1	1	1	–	–	3	–	–	3	3	–	–
Neurotoxicity	–	–	–	–	–	–	–	–	1	–	–	–	1	1	–	–	–	2	–	–	3	–	–	–	3	–	2	–

Table 2. *Toxicities in study III—by dose level*

	Paclitaxel dose (mg/m^2)																											
	135 (n=6)				175 (n=3)				205 (n=6)				230 (n=6)				250 (n=3)				270 (n=6)				290 (n=3)			
Grade	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV
Leucopenia	1	3	–	–	1	–	2	–	1	4	1	–	1	3	2	–	–	2	–	–	2	2	2	–	–	3	–	–
Granulocytopenia	1	–	–	2	–	2	–	1	1	2	–	3	2	1	3	–	–	–	1	1	–	2	–	4	–	–	–	3
Thrombocytopenia	2	–	–	–	1	–	–	–	1	–	–	–	1	–	–	–	–	–	–	–	2	–	–	–	–	–	–	–
Nausea/vomiting	1	2	–	1	2	1	–	–	1	1	–	–	1	1	–	–	2	1	–	–	2	1	–	–	–	–	–	–
Arthralgia	2	–	–	–	1	1	–	–	–	1	1	–	2	–	–	–	–	1	–	–	3	1	1	–	2	–	1	–
Neurotoxicity	–	–	–	–	–	–	–	–	–	–	–	–	2	–	–	–	2	–	–	–	4	–	1	–	1	–	2	–

Table 3. Paclitaxel pharmacokinetics

Dose (mg/m^2)	*n*	AUC (μg/h/ml^{-1})	Clearance (l/h)	Vss (l)
100	3	8.0 ± 2.4	21.90 ± 9.7	121.1 ± 49.2
135	13	11.1 ± 3.1	24.20 ± 7.8	126.4 ± 59.6
175	2	15.6 ± 0.9	21.80 ± 2.1	115.8 ± 29.5
205	3	15.5 ± 3.9	28.00 ± 10.0	93.4 ± 20.5
250	3	21.9 ± 6.9	21.00 ± 3.6	68.4 ± 22.0
270	4	26.5 ± 4.3	17.95 ± 3.7	92.8 ± 47.5
290	7	41.8 ± 11.8	13.90 ± 4.0	77.5 ± 48.4

AUC, area under the curve

patients dosed to a target AUC of 4.0 and the measured AUC was 4.3 mg/ml/min^{-1} in the 9 patients dosed to a target AUC of 4.5. Given the close approximation of target and measured AUCs, it would appear that pretreatment with a 3 h paclitaxel infusion does not alter the expected pharmacokinetics of carboplatin.

The severity of neurotoxicity observed in the 30 patients with NSCLC was correlated with a number of pharmacokinetic parameters, including the total dose of paclitaxel, the paclitaxel C_{max}, the paclitaxel AUC, and the duration of time that the paclitaxel level is greater than 0.05 μM (Figure 1). There was no significant relationship between duration of exposure to levels greater than 0.05 μM and severity of neurotoxicity (Figure 1d). However, the other three parameters did correlate significantly with the grade of neurotoxicity. The most significant pharmacological predictor for severe neurotoxicity was the paclitaxel AUC ($P < 0.0001$). Paclitaxel dose escalation is limited by neurotoxicity. Above a dose of 250 mg/m^2, paclitaxel pharmacology becomes nonlinear as clearance is saturated. Decreasing clearance results in higher paclitaxel AUCs, and the higher AUC is responsible for the enhanced degree of neurotoxicity seen. Unless protection against neurotoxicity can be achieved, further dose escalation of paclitaxel in combination with carboplatin will be difficult.

A phase I study of paclitaxel given as a 1 h infusion together with carboplatin dosed to a target AUC of 4.5 mg/ml/min^{-1} in previously untreated patients is nearing completion. The starting paclitaxel dose for this study was 205 mg/m^2. 3 of 4 patients at this dose level had grade 4 granulocytopenia, 2 had an acute reaction to the paclitaxel infusion, and 1 patient developed grade 3 nausea and vomiting. The dose of

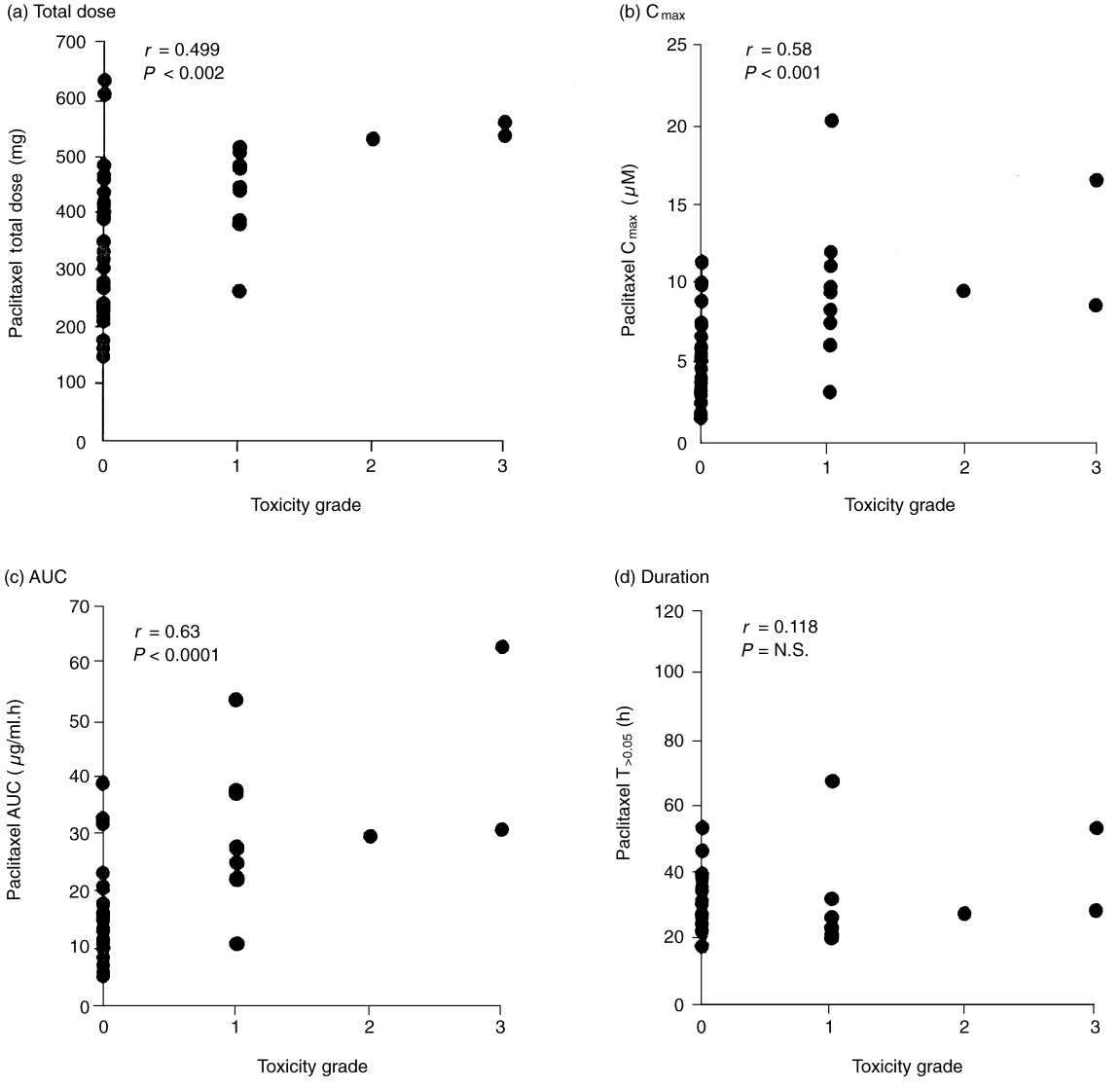

Figure 1. Correlation between paclitaxel dose, pharmacokinetic parameters and neurotoxicity. N.S., not significant.

175 mg/m^2 has been better tolerated, but of 6 evaluable patients at this dose level, there was one grade 3 gastrointestinal toxicity and 1 patient was taken off due to prolonged leucopenia. There has been one response among 8 patients evaluable for response. It does not appear likely that 1 h paclitaxel can be dose escalated when given with low-dose carboplatin and the activity of this regimen at the tolerated doses is disappointing.

CONCLUSION

Since its entry into the clinic 15 years ago, paclitaxel has found uses in a variety of solid tumours. Its novel mechanism as an inhibitor of microtubular disassembly has sparked interest in using it in malignancies refractory to other therapies and in combination with other agents. Paclitaxel has linear pharmacokinetics when given at low to moderate doses, but elimination becomes saturated at high doses. Paclitaxel has activity in advanced cancers of the ovary, breast, lung, head and neck and other sites. Paclitaxel can be given in combination with carboplatin; these agents have non-overlapping toxicities and when given first, paclitaxel does not modify the pharmacokinetics of carboplatin.

76 patients have been treated with paclitaxel and low-dose carboplatin on a series of phase I studies at the Roswell Park Cancer Institute. The MTD of paclitaxel when given with carboplatin dosed to a target AUC of 4.0 mg/ml/min in previously treated patients is 290 mg/m^2 when patients are supported with cytokines. The DLT at this dose is a peripheral sensory neuropathy. The MTD in previously untreated patients without cytokine support is 270 mg/m^2 with carboplatin dosed to a target AUC of 4.5 mg/ml/min. Here too, the DLT is sensory neuropathy. In neither study was there prolonged or cumulative granulocytopenia and in neither study was there significant thrombocytopenia. Responses were seen in 8 patients, including 4 of 25 evaluable patients with advanced NSCLC. There were no responses in lung cancer patients treated with less than 230 mg/m^2 of paclitaxel, but 4 of 16 patients treated with 230 mg/m^2 or more of paclitaxel in combination with carboplatin had a significant clinical response. Pharmacokinetic analysis among the patients with NSCLC found paclitaxel AUC to be the most significant parameter predictive of neurotoxicity. Delayed clearance of paclitaxel at higher doses leads to higher AUCs and more significant neurotoxicity.

It may be possible to treat with higher doses of paclitaxel and carboplatin with the concurrent use of amifostine as a neuroprotectant. Amifostine has been shown to reduce the neurotoxicity related to the administration of cisplatin in a randomised controlled trial conducted by Kemp and colleagues [36]. Amifostine has also been found to be associated with a lower than expected incidence of neurotoxicity related to the use of multiple cycles of high-dose paclitaxel in phase II trials by Spencer and colleagues [37] and by DiPaola and colleagues [38]. Amifostine may modulate the neurotoxicity of paclitaxel by altering paclitaxel pharmacokinetics. Schuller and colleagues [39] noted a 50% increase in paclitaxel clearance and a resulting 29% decrease in the paclitaxel AUC when amifostine is given concurrently with paclitaxel. We have recently initiated a new phase I study of dose escalated paclitaxel given over 3 h in combination with low-dose carboplatin, with amifostine given as a neuroprotectant and with cytokine support. Paclitaxel dosing will start at 270 mg/m^2. To define the pharmacological interaction better, paclitaxel pharmacokinetics will be measured in all patients enrolled on this study and compared with the pharmacokinetics from the paclitaxel/carboplatin studies. Amifostine may also act as a protectant based on modulation of plasma thiols, cysteine and glutathione (GSH), as we have observed a marked modulation of plasma thiols by mesna, another sulphydryl-containing compound. Plasma and peripheral blood lymphocyte cysteine and glutathione will be measured following administration of amifostine.

The combination of paclitaxel and low-dose carboplatin is remarkably well tolerated and can be administered in the outpatient setting to an elderly population. Dose intensive paclitaxel therapy can be given without cytokine support. There is little cumulative granulocytopenia or severe thrombocytopenia seen with even high-doses of paclitaxel. The 3 h paclitaxel infusion appears to be much better tolerated than the 1 h infusion. We are currently studying the activity of paclitaxel and low-dose carboplatin in a series of phase II trials, in patients with small cell lung cancer, head and neck cancer and advanced sarcomas.

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