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Original Paper

Paclitaxel, Cisplatin, Etoposide Combination Chemotherapy: a Multifractionated Bolus Dose Schedule for Non-small Cell Lung Cancer

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In this phase II study, paclitaxel was added to the combination of cisplatin and etoposide (TPE regimen), in 37 patients with advanced non-small cell lung cancer, using a multifractionated dosing schedule. The total dose of paclitaxel (175–200 mg/m^2); cisplatin (75 mg/m^2); and etoposide (175–200 mg/m^2) was divided into five daily doses administered over 3 h with cycles repeated at 21–28 days. 15 patients had stage III A or B disease and 22 stage IV disease. 32 patients were evaluable for toxicity and 37 for response. Neutropenia was the most prominent toxicity. Grade 3 or grade 4 neutropenia was observed in 12 (38%) and 9 (25%) of the patients, respectively and 11 patients required hospitalisation. 3 patients died secondary to chemotherapy related sepsis. Diarrhoea (grade 3, 3 patients; grade 4, 2 patients) was the only other significant non-haematological acute toxicity. The optimal dose rate for this multifractionated regimen was paclitaxel 35 or 40 mg/m^2/fraction; cisplatin 15 mg/m^2/fraction; etoposide 35 or 40 mg/m^2/fraction. Responses were observed in 28 of 37 evaluable patients (3 complete response; 25 partial response [76%]. 22 patients are alive; 8 with stage III B disease received radiation or surgery (3 had minimal or no tumour in the pathology specimen). TPE is a highly active regimen for non-small cell lung cancer and multifractionated dose scheduling is a feasible and well tolerated system.

Key words: multifractionated dose schedule, taxol, platinol, etoposide combination, lung cancer
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INTRODUCTION

THE COMBINATION of paclitaxel (Taxol®; T) with complimentary cytotoxic agents has been a major focus for investigative trials in non-small cell lung cancer (NSCLC) since the widespread availability of this unique microtubule-stabilising plant alkaloid. Combinations of paclitaxel with either cisplatin (Platinol®; P) or carboplatin have been reported most commonly [1, 2]. Although less intensely studied, the combination of paclitaxel with the often-employed combination of cisplatin and etoposide (E) has also been evaluated as the TPE regimen [3–5] alone and in conjunction with radiation [5, 6].

Paclitaxel, although more commonly administered as either a 3 or 24 h infusion cycled every 21 days, has been employed investigationally on a multifractionated schedule on the basis of preclinical data indicating schedule dependency for this agent [7]. Etoposide is usually administered as a daily×5 or on a day 1, 3, 5 schedule because of the superiority of this schedule as defined by randomised trials and its known schedule dependency [8]. Cisplatin, although generally administered as a single day injection, has been delivered via a daily dosing schedule or by infusion in order to minimise the significant nausea associated with its administration and to provide for less cumbersome hydration regimens.

The Cancer Center of Boston initiated a clinical trial of the three drug combination of paclitaxel (T), cisplatin (P) and etoposide (E), employing a unique fractionated dosing schema with five consecutive day fractions repeated at 3 week intervals and/or twice weekly open ended fractions [9]. Patients with NSCLC were treated with the five consecutive day scheme as induction chemotherapy to determine the clinical activity and toxicity of the regimen.

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PATIENTS AND METHODS

Eligibility

Patients with histologically or cytologically confirmed stage III A, B or stage IV NSCLC were entered into the study. All patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 3 or less. Patients with prior chemotherapy or radiation therapy were entered if chemotherapy had been administered more than 6 months prior to entry. Patients were also required to have bidimensionally measurable or evaluable disease. Adequate haematological (total leucocyte count equal to or greater than 4000/μl and platelet count equal to or greater than 100 000/μl), renal (serum creatinine level less than 1.5 mg/dl) and hepatobiliary (total serum bilirubin level less than 1.5 mg/dl) function were also required. Patients with brain metastases were eligible unless active neurological signs or symptoms were present which required urgent radiation therapy.

Pretreatment evaluation consisted of a complete history and physical examination, chest X-ray, complete blood cell count and serum chemistry analysis, including liver profile. Computerised tomographic (CT) scans of the chest, abdomen and pelvis and radionuclide bone scans were performed when clinically indicated. CT scans were also obtained of the central nervous system (CNS) when brain metastases were suspected. All pretreatment blood studies were performed within 4 weeks of initiation of treatment and were repeated prior to each treatment cycle. Radiographic studies were reassessed as indicated by the clinical situation or following every other cycle.

Treatment regimen

The treatment regimen consisted of multifractionated delivery of all three agents administered daily×5, repeated at 21 day intervals [9]. Selected patients were transferred from the multifractionated schedule to administration twice weekly for 3–4 weeks with dose escalation. The transfer was based predominantly on patient convenience in those responding to therapy or to reduce excessive toxicity experienced on the 5 day delivery schedule.

Paclitaxel was administered over the first 1 h period at a dose of 35, 40 or 50 mg/m^2 in 250 ml of normal saline. In the second hour, cisplatin 15 mg/m^2 and etoposide 35, 40 or 50 mg/m^2 were admixed in 500 ml of normal saline and administered. Anti-emetics were administered at the discretion of the primary physician, but generally included the use of oral granisetron 2 mg with or without intravenous dexamethasone 5 or 10 mg. Routine prophylaxis with cimetidine, diphenhydramine and dexamethasone was not employed. Following the initial 5 day cycle, subsequent cycles were repeated at 21 days. For selected patients beginning at day 21, a twice weekly schedule was initiated either on a Monday/Thursday or a Tuesday/Friday pattern with patients receiving each of the three agents at the same daily dose as the induction regimen but with dose escalation carried out for those patients not experiencing grade 3 or greater neutropenia. Dose escalation called for serial increases of both paclitaxel and etoposide (from 35 to 40 or 50 mg/m^2/dose for both agents) while the fractional dose of cisplatin was held constant at 15 mg/m^2 per fraction.

Dose de-escalation was made only for paclitaxel and etoposide with both drug doses equally reduced based upon the level of neutropenia. The objective was to achieve a nadir white blood count between 1000 and 2000 cells/μl. For white blood count nadirs (usually occurring on day 9–11) below 1000 cells/μl, a 25% reduction in paclitaxel and etoposide daily fractionation was made. For white blood count nadirs above 2000/μl, a 20% increment in the daily dose of paclitaxel and etoposide was made.

Response and toxicity criteria

A complete response was defined as resolution of all disease for a minimum of 4 weeks. Partial response required a greater than 50% reduction in the product of the perpendicular diameters of indicator lesions for a minimum of 4 weeks, without the appearance of new lesions. Disease progression was defined as a greater than 25% enlargement of an indicator lesion or development of a new lesion. Stable disease included lesions that did not meet the criteria for response or progression. Toxicities were assessed using the common toxicity criteria guidelines for haematological, renal and gastrointestinal diarrhoea toxicities.

Survival analysis

Survival, time to treatment failure and time to disease progression was measured from the time of initiation of treatment. Response duration was measured from the point at which response was initially identified.

RESULTS

A total of 37 patients were entered into the study. The demographic analysis for all patients is presented in Table 1. Eighty-six per cent of patients had received no prior therapy. The predominant site of measurable disease was the lung reflecting the fact that 41% of the group had stage III A or B disease. 2 patients presented with hypercalcaemia and 3 patients had CNS metastases at presentation. The histological subtypes were distributed typically for NSCLC. More than 50% of patients had a performance status of 2 or 3 (ECOG scale).

Table 1. *Patients characteristics*

Number of patients	37
Age (median) range	66 years (42–78)
Sex	23 males; 14 females
Prior therapy	
Radiation	4 (11%)
Chemotherapy	5 (14%)
None	32 (86%)
Stage	
III A and B	15 (41%)
IV	22 (59%)
Metastatic or measurable sites	
Lung	11 (30%)
Bone	5 (14%)
Central nervous system	3 (8%)
Liver	2 (5%)
Other	3 (muscle 2) (8%)
Histological subtypes	
Squamous cell carcinoma	17 (46%)
Adenocarcinoma	11 (30%)
Large cell carcinoma	8 (22%)
Neuroendocrine	1 (3%)
Performance status	
0–1	16 (43%)
2	16 (43%)
3	5 (14%)

Table 2. Toxicity analysis of the 5 day multifractionated paclitaxel, cisplatin, etoposide (TPE) programme

TPE dose levels (mg/m^2/day)	No. of patients	Neutropenia grade			Anaemia grade		Diarrhoea grade		Hospitalised and/or sepsis
		III	IV	Total (%)	III	IV	III	IV	
35/15/35	15	7	4	(73)	3	0	0	0	5*
40/15/40	15	5	3	(53)	3	0	1	2	6
50/15/50	2	0	1		0	1	2	0	0
Evaluable	32								

*1/5 Died of treatment related sepsis.

A total of 112 courses of therapy were monitored: 85 for the 5 day induction and 20 for the twice weekly schedule. Seven courses of TPE were fractionated over a 3 day period at induction instead of the 5 day period.

A toxicity analysis for the 5 day multifractionated courses is presented in Table 2. 32 evaluable patients received a total of 85 courses at the three dose levels indicated. 5 patients are not included because blood counts were not monitored (3) or the fractionation was over 3 days instead of 5 days (2). At the lowest dose rate of TPE, 73% of patients developed grade 3 or 4 neutropenia and 5 patients required hospitalisation for treatment of neutropenic fever. 1 patient within this group died of treatment related sepsis. At the second dose level for TPE, the incidence of grade 3 and 4 neutropenia was 53% with 6 patients requiring hospitalisation for management of neutropenic fever. The neutropenic nadir occurred at approximately day 9–11 with a median duration of 2 days. Also, at this dose, grade 3 and 4 diarrhoea was observed usually appearing at day 6; 2 patients required hospitalisation for intravenous hydration. Only 2 patients were monitored at the highest dose level; one developed grade 4 neutropenia and both developed grade 3 diarrhoea.

9 of the 32 patients were transferred to a twice weekly schedule at the same or higher fractionation dose for the induction phase. 2 patients received TPE twice weekly at 35, 15 and 35 mg/m^2; 5 patients at 40, 15 and 40 mg/m^2 and 2 at 50, 15 and 50 mg/m^2 per dose. 5 of the 9 developed grade 3 neutropenia and of the 5, 1 died from complications secondary to treatment related sepsis. None of the patients developed grade 4 neutropenia. The majority of patients receiving therapy for three or more cycles developed grade 3 anaemia requiring red cell transfusion or erythropoietin or both.

Tumour response was evaluable in all 37 patients (Table 3). 28 of 37 patients (76%) achieved a response by objective criteria including three complete responses and 25 partial responses. The response rate was higher in stage III disease (87%) compared with stage IV disease (68%). There were no differences in response with regard to the histological subtypes. Responses relative to metastatic site were notable for responses in CNS lesions for 3 patients.

Survival for the group has not yet reached a median level with a minimum follow-up from entry of 6 months with an overall survival range of 1–17 + months. 15 of the 37 patients have died. The median survival of patients within the responding group has not been reached at 6 + months with a range of 1–17 + months. For non-responders, all of whom have died, the median survival was 7 months (range 2 weeks to 12 months). Of the 15 patients who have died, 3 were treatment related deaths (1 in a patient who had achieved a partial response) and 10 patients have died with CNS metastases.

Of the 22 patients who remain alive, 13 are continuing on therapy. 7 of 22 (32%) are without evidence of disease following radiation alone (1) or radiation followed by surgery (7 patients). In 7 patients who had surgery, 3 had no evidence of tumour, 3 had minimal viable tumour (< 1 cm) and 1 had extensive local mediastinal tumour in lymph nodes.

DISCUSSION

Advances in lung cancer management have been heralded by the introduction of new chemotherapeutic agents and new combinations of agents. Livingston summarised the evolution of combination chemotherapy for NSCLC in 1994, emphasising the importance of the development of new agents to be introduced into multi-drug combinations [10]. Table 4 summarises the activity for some of these new agents in NSCLC as well as a selection of platinum based combination regimens [1, 2, 11–18]. These selected regimens serve as a useful perspective for the results of the present study, recognising that many clinical factors influence the reported results and that studies are heterogenous with regard to patient selection (histological subtypes, stage III, IV or both); metastatic sites

Table 3. Response and survival data: paclitaxel, cisplatin, etoposide (TPE) analysis in non-small cell lung cancer

Overall response	
Partial response	25/37
Complete response	3/37
Total	28/37 (76%)
No response progressive disease	9/37
Response according to stage	
Stage III	13/15 (87%)
Stage IV	15/22 (68%)
Response according to histological subtype	
Epidermoid	13/17 (76%)
Adenocarcinoma	8/11 (73%)
Large cell	6/8 (75%)
Neuroendocrine (non-small cell)	1/1
Response according to metastatic site	
Lung	3/11
Liver	1/1
Central nervous system	3/3
Survival	
All patients	
Median	6 + months
Range	1–17 + months
Responders (28)	
Median	6 + months
Range	1–17 + months
Non-responders (9)	
Median	7 months
Range	2 weeks to 12 months

Table 4. *A selected listing of antitumour activity for new single agents; platinum-based combinations; and paclitaxel plus platinum combination chemotherapy in non-small cell lung cancer*

Drug regimen	Response rate (%)
Single new drugs	
Paclitaxel [11]	24
Topotecan [12]	15
Vinorelbine [13]	12–31
Gemcitabine [14]	22
Platinum-based combinations	
Vinblastine, cisplatin, amifostine [15]	64
Cisplatin, ifosfamide, etoposide or vinblastine [16]	25–29
Vinorelbine, cisplatin [17]	30
Paclitaxel and platinum analogues	
Paclitaxel + cisplatin [1]	26.5–32.1
Paclitaxel + carboplatin [2]	62
Paclitaxel + carboplatin [18]	62

(with or without CNS metastases); multi versus single institution, etc.

None the less, some general comments on the above studies may be useful. Four new single agents have been or are in the process of being evaluated and in fact, in previously untreated patients antitumour activity, although modest, ranges between 12 and 24%. The selected platinum based combination chemotherapy regimens in Table 4 are illustrative of the spectrum of agents used in conjunction with platinum, particularly plant alkaloids, with only a slight increase in response rate over single agents, except for one report of combined vinblastine, cisplatin with the chemoprotective agent Amifostine. The combination of the taxane, paclitaxel, with either cisplatin or carboplatin is the most frequent combination being evaluated at the present time and response rates, particularly with carboplatin, have been reported as high as 62%. In the majority of studies, patients with both stage III and IV disease are included.

The present study of TPE represents a logical extension of the paclitaxel–cisplatin trials, employing a unique multifractionated schedule. Previous studies at our institution have utilised such schedules for single agent paclitaxel [7] in addition to infusional cisplatin [19] and etoposide [20] with the infusion acting as a type of multifractionated therapy.

Three previous studies have addressed the use of TPE in NSCLC utilising different schedules and different dose intensities than those employed in the present study. In a study from the MD Anderson Cancer Center [3], the response rate to TPE in NSCLC was 45% in 24 patients. The paclitaxel and cisplatin doses were not fractionated and granulocyte colony stimulating factors (G-CSF) was routinely employed. In a Cleveland Clinic study, responses in the phase I study were observed in 7 of 8 patients [4] with small cell carcinoma and the paclitaxel and etoposide doses were substantially less than the present study, in spite of the use of G-CSF. Finally, a phase II trial in stage III NSCLC reported two studies in which paclitaxel was administered as a 1 h infusion at a low-dose in combination with cisplatin and etoposide [5, 6].

In contrast to these previously reported TPE studies, the present study, utilising a multifractionated schema for all three agents, achieved a high response rate in a group of patients with either stage III or stage IV disease (response rate 77%). Dose intensity was higher for all three agents compared with the previously cited three trials without the necessity for G-CSF [9].

The TPE combination appears to be highly effective in advanced NSCLC and multifractionation dose scheduling appears to provide a favourable toxicity profile. In spite of the encouraging results, there are several unanswered questions about the combination that should be addressed in future clinical trials. It would be important, before adopting such a distinctive drug administration schedule, to investigate the significance of multifractionation as compared with a TPE combination utilising single day paclitaxel and cisplatin administration. The use of five consecutive day dose fractions cycled at 3 week intervals versus a twice weekly schedule may have different toxicity profiles. The haematological toxicity observed in this phase II trial was substantial in that a large proportion of patients developed leucopenia and/or sepsis and 11 required hospitalisation. Cytokines were not employed routinely prophylactically and may be indicated to maintain dose intensity. The brief nadir duration without cytokine support is noteworthy, as is the common use of erythropoietin, related presumably to the platinum associated anaemia. The specific contribution of each of the component drugs of TPE should also be addressed. For example, the role of etoposide in NSCLC is still undefined, although it is clearly synergistic with cisplatin in experimental systems. However, it contributes substantially to the haematopoietic toxicity of the combination and its additive therapeutic benefit may be questioned. A comparative trial of paclitaxel plus cisplatin with or without etoposide may be considered an important avenue of investigation.

Another issue which could be addressed revolves around the particular platinum analogue to be utilised. Cisplatin and carboplatin have different toxicity patterns, with carboplatin adding significantly to the haematopoietic toxicity. Studies comparing cisplatin and carboplatin have suggested that cisplatin may be more active relative to carboplatin but with greater non-haematopoietic toxicity in some tumours [21].

In addition to comparative trials to address the above issues, the introduction of the new agents into a combination of paclitaxel and a platinum analogue would be worth pursuing. Specifically, the addition of vinorelbine to a combination of paclitaxel and cisplatin using a multifractionated dose schema would be a reasonable next step in phase I–II trials.

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