Pergamon

*European Journal of Cancer*, Vol. 34, No. 5, pp. 664–667, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(97)10108-3

## Original Paper

# Paclitaxel, Cisplatin and Etoposide Combination Chemotherapy: a Comparison of Dose Intensity in Two Multifractionated Dose Schemas

J. Lokich, N. Anderson, C. Moore, M. Bern, F. Coco, H. Sonneborn, E. Dow and D. Strong

The Cancer Center of Boston in Boston, Plymouth and Framingham, 125 Parker Hill Avenue, Boston, Massachusetts 02120, U.S.A.

**66 patients with a variety of tumour types received the multifractionated TPE three drug regimen in a non-random allocation as a 5 day schedule (schedule A) or as a twice weekly schedule (schedule B). The dose per fraction for each component drug was 35, 40 or 50 mg/m$^2$ for both paclitaxel and etoposide and for cisplatin, the dose per fraction was 15 mg/m$^2$. The total paclitaxel and etoposide dose was 175, 200, 250 mg/m$^2$ 3 week cycle. For schedule A, grade 3 or 4 neutropenia was observed in 70/114 cycles (61%) with two treatment related deaths from 50 treated patients. For schedule B, grade 3 neutropenia was observed in 1 of 30 courses (3%) with one drug related death from 19 treated patients. Dose intensity was increased by 20% for both paclitaxel and etoposide with the twice weekly schedule and at all dose levels, with haematological toxicity substantially reduced relative to schedule A. Using multifractionated schedules, a twice weekly open ended schedule results in an approximately 20% greater dose intensity and less toxicity compared with a 5 day schedule repeated every 3 weeks. The recommended dose schedule for TPE is paclitaxel 40 mg/m$^2$; cisplatin 15 mg/m$^2$ and etoposide 40 mg/m$^2$ twice weekly for 3 weeks repeated every 4 weeks.** 

**Key words: multifractionated dosing schedules, paclitaxel based combination**
*Eur J Cancer*, Vol. 34, No. 5, pp. 664–667, 1998

## INTRODUCTION

COMBINING PACLITAXEL (T), cisplatin (P) and etoposide (E) into a three drug regimen has been explored utilising a variety of doses and regimens for the component drugs [1–3]. Most commonly, paclitaxel is administered as a 3 or 24 h infusion and cisplatin as a 2 h infusion with etoposide administered over 3 days; cytokines are commonly utilised to increase the tolerated dose. Fractionating paclitaxel for a 3 or 5 day schedule has provided the capability of increasing the maximum tolerated dose for this agent without the need for cytokine support [4]. The optimal schedule for paclitaxel administration continues to be controversial, with weekly and 96 h infusional schedules being explored.

We developed two dose schedules for a three drug regimen integrating paclitaxel, cisplatin and etoposide while fractionating each of the component drugs on either a 5 day regimen repeated at 21 day intervals or a twice weekly regimen administered for a minimum of 3 weeks to a maximum of 7 weeks. In this non-randomised programme, we analysed the data to compare the tolerance and dose intensity of the two schedules.

Correspondence to J. Lokich.
Received 2 Jul. 1997; revised 6 Oct. 1997; accepted 29 Oct. 1997.

## PATIENTS AND METHODS

*Patient eligibility*

Patients with histologically or cytologically confirmed advanced cancer who were over the age of 18 years were eligible. Patients may have had prior chemotherapy and no specific restrictions as to tumour type were established, although lung and breast cancer were the predominant tumours in 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 were entered into the study if chemotherapy had been administered more than 6 months prior to entry. Patients were also not required to have measurable disease, but adequate haematological (white blood cell count $\geq 4000/\mu l$ and platelet count $\geq 100\,000/\mu l$) function was required. A

creatinine level less than 1.5 mg/dl and a bilirubin level less than 1.5 mg/dl were also necessary. Patients with brain metastases were eligible unless active neurological signs or symptoms were present that 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 the liver profile. Computerised tomographic (CT) scans of the chest, abdomen and pelvis, as well as radionuclide bone scans, were performed when clinically indicated. CT scans were obtained of the central nervous system (CNS) when brain metastases were suspected. All pretreatment studies were performed within 4 weeks of the initiation of treatment and were repeated prior to each treatment cycle.

*Treatment regimen*

The treatment regimen consisted of multifractionated delivery of all three agents (paclitaxel, cisplatin and etoposide) administered according to two schedules. The trial was not randomised. Initial patient entries were placed on a 5 consecutive day treatment regime and after 50 patient entries, the twice weekly schedule was employed. In addition, some patients were changed to the twice weekly schedule for patient convenience. The specific dose schedules are designated as A and B (Figure 1). Schedule A was defined as five daily administrations repeated at 21 day intervals and schedule B as twice weekly administration with therapy initiated on either a Monday/Thursday or a Tuesday/Friday pattern. Patients received the paclitaxel, cisplatin and etoposide in both schedules using the same daily dose rate for each of the component drugs.

Paclitaxel was administered first in the sequence at a dose of 35, 40 or 50 mg/m$^2$ infused in 250 ml of normal saline over 1 h. Cisplatin 15 mg/m$^2$ and etoposide 35, 40 or 50 mg/m$^2$ were admixed in 500 ml of normal saline and administered over the second hour. Anti-emetics were administered at the discretion of the physician, but generally included the use of oral granisetron 2 mg with or without dexamethasone 5 or 10 mg intravenously. No patient received routine cimetidine of diphenhydramine. Dose escalation was carried out for those patients not experiencing neutropenia, to a maximum dose for the twice weekly regimen for paclitaxel and etoposide of 50 mg/m$^2$ dose.

Dose adjustments were made only for paclitaxel and etoposide and were based on the degree of leucopenia. The objective was to achieve a nadir total white blood cell count between 1000 and 2000 cells/μl (grade 3). For white blood cell count nadirs (usually on day 9–11) below 1000 cells/μl (grade 4), a 25% reduction in the paclitaxel and etoposide daily dose was made. For white blood cell count nadirs above 2000 (grade 2), a 20% increment in the daily dose of paclitaxel and etoposide was made.

Haematopoietic growth factors were not routinely administered but were employed at the discretion of the treating physician. In general, granulocyte colony stimulating factors (G-CSF) and granulocyte–macrophage colony stimulating factor (GM–CSF) were not administered, but erythropoietin was commonly used for haemoglobin levels of less than 9.5 g%.

*Response and toxicity criteria*

A complete response was defined as resolution of all disease for a minimum of 4 weeks. A partial response required a greater than 50% reduction in the sum of the products of the greatest cross-section or 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 toxicities.

*Dose intensity comparative analysis*

In order to compare dose intensities across the two dose schedules (five daily doses versus twice weekly doses), dose intensity was calculated on the basis of the mg/m$^2$/week formula. Total doses per cycle were calculated for the 5 day regimen and divided by the weeks of interval between cycles. For the twice weekly regimen, a minimum cycle duration was 3 weeks and the calculated dose intensity represented that amount of drug administered on the 2 days per week that therapy was delivered.

| | | | | |
|---|---|---|---|---|
| Schedule A | Week | 1 | | 4 |
| | Day | d1–d5 | | d28–d32 |
| Dose / fraction | Paclitaxel | 40 mg/M$^2$/day | Total dose / cycle | 200 mg/M$^2$ |
| | Cisplatin | 15 mg/M$^2$/day | | 75 mg/M$^2$ |
| | Etoposide | 40 mg/ M$^2$/day | | 200 mg/M$^2$ |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Schedule B | Week | 1 | | | 2 | | 3 | |
| | Day | 1 | 4 | 8 | 11 | 15 | 18 | Rest 1–2 weeks |

| | | | | |
|---|---|---|---|---|
| Dose / fraction | Paclitaxel | 40 mg/M$^2$/day | Total dose / cycle | 200–250 mg/M$^2$ |
| | Cisplatin | 15 mg/M$^2$/day | | 75 mg/M$^2$ |
| | Etoposide | 40 mg/ M$^2$/day | | 200 mg/M$^2$ |

**Figure 1. Treatment Scheme for schedule A and schedule B.**

## RESULTS

A total of 66 patients were entered into the study between January 1995 and October 1996 (Table 1). The major tumour category was lung cancer within which 39 patients had non-small cell and 7 patients small cell carcinoma. 49 of the 66 patients had not received any prior therapy. Performance status was 3 or greater in only 3 of the 66 patients.

57 (86%) of the 66 patients entered into the study were evaluable for haematological toxicities. Of the 9 other patients, 1 had had a prior bone marrow transplant and had limited marrow reserve and in 8 patients the blood counts were not consistently available. All patients were evaluable for non-haematological toxicities and all patients were evaluable for response, with the exception of 2 patients who had no measurable disease. The data for haematological toxicity for the two separate groups are detailed in Table 2. 50 patients were treated with the 5 day schedule (schedule A) repeated at 3 week intervals in whom 114 cycles were analysed. 19 patients were treated with the twice weekly schedule (schedule B) for a total of 30 evaluable courses. 13 patients received sequentially the 5 day cycle followed by the twice weekly schedule.

As indicated in Table 2, grade 3 and grade 4 neutropenia occurred predominantly in those patients in schedule A. At the lowest dose rates for paclitaxel, cisplatin and etoposide, grade 3 or grade 4 neutropenia developed in 66% of courses. At the higher incremental dose level, grade 3 or 4 neutropenia was observed in 30/52 courses (58%). Two drug related deaths were identified on the 5 day schedule and a total of 7 of 38 patients were hospitalised for neutropenic fever or diarrhoea (18%). In schedule B, only one course was associated with grade 3 neutropenia but there was 1 drug related death in the 19 entered patients with 2 patients requiring hospitalisation for fever or diarrhoea.

*Tumour response*

The broad spectrum of tumours entered into the trial focused on lung cancer. In non-small cell lung cancer, 28 of 37 patients demonstrated a response (3CR, 25PR) and in the small cohort of small cell lung cancer, 7 (4CR, 3PR) of 7 patients responded, although 5 of the 7 have subsequently relapsed. 5 of 5 patients with ovarian cancer have responded, with 3 complete responders. For breast cancer, the majority had received prior therapy, but there were 5 of 7 partial responses, including a patient with a prior bone marrow transplant. In oesophageal cancer, 4 of 4 responded (all PR).

*Table* 1. *Patient characteristics*

| | |
|---|---|
| Total number of patients | 66 |
| Age median (range) | 65 years (40–80) |
| Sex (male: female) | 35:31 |
| Tumour categories | |
| Lung cancer | 46 |
| non-small cell | 39 |
| small cell | 7 |
| Breast | 7 |
| Oesophagus | 4 |
| Head and neck | 1 |
| Bladder | 1 |
| Unknown primary | 2 |
| Ovary | 5 |
| Prior therapy | |
| None | 49 |
| Radiation | 4 |
| Chemotherapy* | 15 |

*Bone marrow transplant (1 patient).

*Table* 2. *Graded haematological (neutropenia) toxicity related to dose and schedule**

| TPE (mg/m$^2$/dose) | | | Number of | No. of | Neutropenia grade | | | | |
|---|---|---|---|---|---|---|---|---|---|
| T | P | E | patients | cycles | 0 | 2 | 3 | 4 | 5 |
| Schedule A | | | 50 | | | | | | |
| 40 | 15 | 40 | | 52 | 7 | 14 | 20 | 10 | 1 |
| 35 | 15 | 35 | | 59 | 8 | 11 | 23 | 16 | 1 |
| Schedule B | | | 19 | | | | | | |
| 50 | 15 | 50 | | 10 | 7 | 3 | — | — | — |
| 40 | 15 | 40 | | 11 | 3 | 6 | 1 | — | 1 |
| 35 | 15 | 35 | | 9 | 9 | — | — | — | — |

*Schedule A, 5 day regimen repeated every 3 weeks; schedule B, twice weekly regimen repeated for 3–7 weeks.
T, paclitaxel; P, cisplatin; E, etoposide.

*Dose intensity*

The specific comparison of dose intensity each dose level and across the two multifractionated regimens are listed in Table 3. At all dose levels, the twice weekly schedule resulted in a 20% increase in dose intensity. At the highest dose level, no patients were evaluable for neutropenia, but 2 patients developed grade 3 diarrhoea on the 5 day cycle off study and no further patients were entered at this dose level. It is, therefore, unlikely that the dose fractions for TPE on the 5 day cycle could be increased beyond the dose intensity for paclitaxel and etoposide of 66 mg/m$^2$/week. In contrast, the dose intensity for the twice weekly schedule is at least 80 mg/m$^2$ for paclitaxel and etoposide and is commonly 100 mg/m$^2$/week for selected patients. This study does not address the issue of optimal sequencing of delivery of the component drugs which is a point that has been emphasised as important in recent studies.

## DISCUSSION

The combination of paclitaxel with a platinum analogue is being explored extensively in phase I, II and III trials with and without the addition of etoposide and with or without the use of prophylactic cytokines to protect against severe neutropenia. The rationale for combining these agents into a

*Table* 3. *Comparison of dose intensity for* 5 *day and twice weekly regimens relative to dose per fraction*

| | TPE dose (mg/m$^2$/dose) | | | | Dose intensity (mg/m$^2$/week) | | | Dose intensity difference |
|---|---|---|---|---|---|---|---|---|
| Level | T | P | E | Schedule | T | P | E | (%) |
| 1 | 35 | 15 | 35 | A | 58 | 25 | 58 | 20 |
| | | | | B | 70 | 30 | 70 | |
| 2 | 40 | 15 | 40 | A | 66 | 25 | 66 | 21 |
| | | | | B | 80 | 30 | 80 | |
| 3 | 50 | 15 | 50 | A | 83 | 25 | 83 | |
| | | | | B | 100 | 30 | 100 | 20 |

three drug regimen relates to the synergy observed in experimental systems for platinum and etoposide and the overlapping spectrum of antitumour activity; distinctive mechanisms of tumour cell kill and minimal overlapping host toxicity. The rationale for the two schedules selected in the present study is based in part on (a) the known schedule dependency for paclitaxel and for etoposide and (b) the elimination of the need for complex hydration regimens for higher cisplatin doses. Multifractionation or the use of multiple bolus dosages over time addresses the schedule dependency issue for optimising the effectiveness of paclitaxel and etoposide without the use of cumbersome infusion delivery systems. The concept of cycling therapy for a 5 day course every 3 weeks is most commonly employed, but the introduction of a twice weekly regimen was designed to promote patient convenience and reduce toxicity while maintaining efficacy. Furthermore, the twice weekly schedule extends the frequency of tumour exposure to cytotoxic drugs. In this study, the twice weekly schedule resulted in an increase in dose intensity and, paradoxically, a concomitant decrease in toxicity. Multifractioned dose scheduling may have some important practical advantages as applied to paclitaxel based combinations in particular, but may be useful in other regimens as well. The first three advantages are reflected in the data of this study. In addition, at a practical level, the twice weekly schedule provides the capability of interrupting or deleting a fraction in the event that an early toxicity is identified, precluding the development of severe or life threatening toxicities.

Conclusions for this study are limited because of the heterogeneity of the patient population and by the non-randomised nature of the study which does not allow the two groups to be compared in terms of potential superiority of one over the other. None the less, the data supports the concept that the twice weekly schedule for TPE (a) increases the dose intensity for paclitaxel and (b) does not require cytokine support. The possibility of increasing the dosage per fraction on the twice weekly regimen because of the absence of neutropenia could be raised but was not pursued in this study in favour of prolonging the treatment interval beyond 3 weeks. Selected patients were treated for as long as 7 consecutive weeks at the dose fractions of paclitaxel 50 mg/m$^2$; cisplatin 15 mg/m$^2$ and etoposide 50 mg/m$^2$. Another reason for not increasing the dose fraction, in spite of the absence of neutropenia, relates to the potential problem of non-haematological toxicity, such as diarrhoea and the possibility of cumulative neurotoxicity.

The large number of clinical responses is most probably related to the fact that the patients had good performance status, the majority had not received prior therapy and the major tumour types (lung, breast, ovary) were those recognised to be chemotherapy responsive. The possibility exists that a synergistic interaction between the drugs led to the high frequency of tumour response, but this issue would need to be addressed in a specifically designed phase III trial.

Future studies of multifractionated TPE could address introducing an additional potentially synergistic agent, such as vinorelbine, or doing comparative trials to establish definitively the preferable schedule and/or the specific role of the individual component drugs.

1. Murphy WK, Huber M, Fossella FV, *et al.* Phase I study of taxol (T), cisplatin (P) and etoposide (E) with G-CSF (G) in patients (PTS) with non-small cell lung cancer (NSCLC). *PASCO* 1995, **14**, 354 (#1076).
2. Levitan N, McKenney J, Tahsildar H, *et al.* Results of a phase I dose escalation trial of paclitaxel, etoposide and cisplatin followed by filgrastim in the treatment of patients with extensive stage small cell lung cancer. *PASCO* 1995, **14**, 379 (#1177).
3. Greco FA, Stroup SL, Gray JR, Hainsworth JD. Paclitaxel in combination chemotherapy with radiotherapy in patients with unresectable stage III non small cell lung cancer. *J Clin Oncol* 1996, **14**, 1642–1648.
4. Lokich J, Anderson N, Bern M, *et al.* Multi-day fractionated administration schedule for paclitaxel. *Ann Oncol* 1995, **6**(9), 883–886.

**Acknowledgement**—Supported in part by The Cancer Center Research Foundation.