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Phase II Study of Weekly 5-Fluorouracil, Cisplatin and Vinblastine in Advanced Non-small Cell Lung Cancer

Peter J. O'Dwyer, Corey J. Langer, Judy Walczak, Michael H. Levy, Kristin Padavic-Shaller, Gary R. Hudes, Sam Litwin and Robert L. Comis

The scheduling of chemotherapeutic agents may be important in optimising their antitumour actions. This has been explored in non-Hodgkin lymphoma, osteogenic sarcoma and bladder cancer with improved results using intensive, weekly dosing schemas. We began a phase II study of cisplatin, 5-fluorouracil and vinblastine in non-small cell lung cancer (NSCLC) on a weekly schedule. 38 patients with advanced or metastatic NSCLC were entered; 32 are evaluable for response. 11 patients were treated with 5-fluorouracil 1.5 g/m^2 and vinblastine 4 mg/m^2 by 24-h continuous infusion, and cisplatin 30 mg/m^2 over 30 min, 6–8 h after the start of the infusion. Because of prohibitive myelotoxicity, the next 27 patients received 5-fluorouracil 1.2 g/m^2 and vinblastine 3 mg/m^2. None had had prior chemotherapy while 6 had had previous radiation therapy. Myelosuppression was the predominant toxic effect. Other side-effects included neuropathy, diarrhoea, mucositis, nausea and vomiting. 32 patients are evaluable for response: there have been 14 partial remissions (44%). Responses have occurred chiefly in lung and lymph nodes. The median survival on this study is 7 months, and responders did not live longer than non-responders. While this regimen is well tolerated by the majority of patients and has a response rate comparable to other active regimens identified in single institution studies, survival does not appear to be enhanced. We conclude that the schedule manipulation described here does not enhance the therapeutic index of these drugs in NSCLC.
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INTRODUCTION

THE DEVELOPMENT of chemotherapy regimens for the treatment of advanced non-small lung cancer (NSCLC) has progressed slowly over the past 10 years. Cisplatin, the most active single agent, is incorporated in a variety of combination regimens, the best of which include either a vinca alkaloid or etoposide. Response rates of the order of 40–50% are obtained with cisplatin-containing regimens in single institution studies [1, 2]; such regimens generally yield rates closer to 25 to 30% in larger Cooperative Group trials [3–5]. Despite these modest response rates, a randomised study of cisplatin/vindesine vs. best supportive care has shown a clear survival benefit over untreated controls [6]. Thus there are indications that pursuing further the chemotherapy of NSCLC may provide incremental gains in response and survival.

The issue of drug scheduling is an aspect of the design of chemotherapy regimens which has received little attention in NSCLC. Many chemotherapeutic drugs, including antimetabolites, vincas and epipodophylotoxins demonstrate schedule dependency in preclinical models [7]. In recent years, promising regimens using unconventional schedules have been developed in bladder cancer [8], non-Hodgkin lymphoma [9], and osteo-

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genic sarcoma [10]. A common characteristic of all of these regimens is the use of weekly chemotherapy at substantial doses.

We designed a phase II study incorporating two active agents, vinblastine and cisplatin, in the treatment of NSCLC to investigate the effects of drug scheduling in this disease. 5-fluorouracil, though described as having modest activity as a single agent in NSCLC [11, 12], adds substantially to the activity of cisplatin in other diseases. Moreover, combination regimens incorporating 5-fluorouracil are active [13, 14]. It has recently become apparent that high doses of 5-fluorouracil are well-tolerated on a 24 hour continuous infusion schedule, repeated weekly. Doses as high as 2600 mg/m^2 may be safely administered either alone or in combination with the biochemical modulator PALA [15, 16]. The pronounced activity of regimens incorporating 5-fluorouracil given on this schedule prompted its inclusion in this regimen for NSCLC.

PATIENTS AND METHODS

Eligibility

From July 1987 to August 1989, 38 patients with histologically documented recurrent or metastatic NSCLC were entered in this study. Eligible patients were required to have no prior cytotoxic chemotherapy, to be of good performance status (0-1 ECOG), and to have bidimensionally measurable disease (clearly defined on X-ray or scan in two dimensions, and not within the portal of previous radiation). Patients had normal bone marrow (white cell count $\geq$ 4000 μl; platelets $\geq$ 100 000 μl), kidney (serum creatinine $\leq$ 1.5 mg/dl), and liver (bilirubin $\leq$ 2 mg/dl) function. Patients with brain metastasis were not eligible. The goals and conduct of this study were explained to all patients, who signed written informed consent in accordance with federal, state and institutional guidelines.

Drug treatment

Patients were admitted to hospital the morning of their treatment; most had a double-lumen catheter placed in a central vein before beginning on study. The regimen consisted of 5-fluorouracil and vinblastine administered separately though a Y-connector by 24-h continuous infusion. Cisplatin 30 mg/m^2 was administered as a 30-min bolus 6–8 h following the initiation of the 24-h infusion. Patients were hydrated with 2 l of saline or dextrose saline, and received furosemide 40 mg IV and mannitol 12.5 g IV prior to cislatin. Antiemetic therapy with three drugs (usually prochlorperazine, lorazepam and dexamethasone) also preceded cisplatin administration, and hydration was maintained intravenously until the patient was discharged. The first 11 patients treated on this study received 5-fluorouracil 1.5 g/m^2 and vinblastine 4 mg/m^2 by 24-h infusion. Unacceptable myelosuppression led to a dose reduction; the subsequent 27 patients received 5-fluorouracil 1.2 g/m^2 and vinblastine 3 mg/m^2. Courses were repeated weekly.

Doses were modified for toxicity, which was graded using the Common Toxicity Criteria (NCI, Bethesda). For white cell counts $<$ 3500 μl and/or platelet counts $<$ 75 000 μl, a 50% reduction was made in vinblastine and 5-fluorouracil doses. For white cell counts $<$ 1500 μl and/or platelet counts $<$ 50 000 μl, vinblastine was held and 5-fluorouracil reduced by 50%. The 5-fluorouracil dose was also reduced by 50% for grade 2 mucositis, and the cisplatin dose reduced by 50% if the serum creatinine rose above 1.5 mg/gl. Grade 3 or 4 toxicity led to the temporary suspension of these drugs. Similar dose modifications were undertaken for neurotoxicity, or hand–foot syndrome. Pretreatment evaluation consisted of a history and physical examination, complete blood count, serum chemistry panel, serum electrolytes and creatinine, urine analysis and appropriate X-rays and scans as needed for disease measurement. A complete blood count and serum electrolytes and creatinine were obtained weekly. History and physical examination, serum biochemistry screen, and X-rays and scans were repeated every 4 weeks. Patients who went off study were followed long-term for adverse events.

All patients who received any treatment were evaluable for toxicity. Patients who received a minimum of four weekly treatments were evaluable for response, unless progressive disease was evident. Response definitions were standard: a complete response was defined as the complete disappearance of all objective evidence of disease (clinical and radiological) for a minimum of 4 weeks; a partial remission was defined as a 50% or greater decrease in the sum of the products of the perpendicular diameters of measurable lesions; a minor response was a 25–50% decrease in the sum of the products of the perpendicular diameters of measurable lesions; stable disease was defined as a steady state of response with less than a 25% increase or decrease in measurable lesions for a minimum of 6 weeks with the appearance of no new lesions [17]. Progressive disease was defined as an increase of at least 25% in the size of any measured lesion or the appearance of new lesions. Response was assessed by the treating physician and the principal investigator separately. Survival duration was measured from the first day of treatment until the day of death. Response duration was measured from the date of documentation of a partial remission until relapse. The survival curve was plotted by the technique of Kaplan and Meier [18].

RESULTS

Patient's characteristics

38 patients were entered of whom 32 are evaluable for response. The demographic characteristics of the patients entered on the study are shown in Table 1. 6 patients were inevaluable for response. In 1, the lesion being followed was found to be non-malignant. 1 patient presented with a new brain metastasis 1 week after receiving first cycle of therapy. 1 patient had a cardiopulmonary arrest, believed secondary to myocardial infarction and 1 patient a pulmonary embolism after one treatment. 1 patient developed severe ataxia after a single dose of treatment and was taken off study. 1 patient died of pneumonia, in the absence of myelosuppression, after 3 weeks of treatment. Of the patients evaluable for response, all were of good performance status, though most were symptomatic from their disease. The preponderance of adenocarcinoma is consistent with experience elsewhere.

An analysis of toxicity was performed after the entry of 9 patients. The toxicity experienced by this group of patients is shown in Table 2. 5 patients experienced grade 4 granulocytopenia and/or leukopenia. In 1 patient, this toxicity was accompanied by grade 4 diarrhoea. The incidence of nausea and vomiting was also excessive for a weekly regimen. Based on these findings, the dose of vinblastine was reduced to 3 mg/m^2 and that of 5-fluorouracil to 1.2 g/m^2, both by 24-h continuous infusion weekly. The dose of cisplatin was not changed.

This modification yielded a regimen which was much better tolerated, as shown in Table 3. No subsequent patient had grade 4 myelosuppression and gastrointestinal toxicity was moderate. Among patients who received protracted courses of treatment, neurotoxicity (mainly in the form of paresthesias) supervened but was not severe. This dose modification did not influence the

Table 1. Demographic characteristics of treated patients

Patients entered/evaluable	38/32
Male/female	25/13
Median age (range)	59 (34–77)
Performance status	
0	9
1	29
Stage	
IIIB	12
IV	26
Histology	
Adenocarcinoma	25
Squamous cell	7
Large cell	4
Bronchoalveolar	1
Unclassified	1
Metastatic sites	
Lung	26
Nodes	
Mediastinal/hilar	16
Other	9
Liver	11
Bone	8
Adrenal	2
Prior therapy	
Surgery	9
Radiation	6
None	27

number of treatments tolerated by patients on this study. At the higher doses, the median number of cycles administered was nine (range 1–39), while at the reduced dose, the median number of cycles was 10 (range 1–40).

Among the 32 patients evaluable for response there were 14 partial remissions (44%), and 2 minor responses. Inclusion of all patients entered in the denominator gave a response rate of 36%. The median duration of response among the patients with partial responses was 4 months (range 1–14 months). In addition, 12 patients had stable disease lasting for a median of 7 months (range 2.5 to 22+ months). The Kaplan–Meier survival curve for all patients entered on this study is shown (Fig. 1). The actual median survival was 7 months. An analysis of survival of evaluable patients was instructive: the median survival of patients with partial response was 7.2 months while that of all other evaluable patients was 6.5 months, an insignificant difference. This comparison indicates that despite the relatively high response rate for a phase II trial, response does not appear to confer an advantage in survival.

The sites of responding lesions included lung (both primary and secondary) in 9 patients, lymph nodes in 9 patients, and liver in 1 patient.

Table 2. Toxicity

		Grade				
		0	1	2	3	4
Leukopenia	9	0	1	4	2	2
Granulocytopenia	9	1	0	3	0	5
Thrombocytopenia	9	7	2	0	0	0
Mucositis	9	5	1	3	0	0
Diarrhoea	9	7	1	0	0	1
Paresthesia	9	6	2	1	0	0
Nausea	9	2	5	0	2	0
Vomiting	9	0	3	5	1	0

No. of patients.

9 patients were treated with 5-fluorouracil 1.5 g/m², and vinblastine (4 mg/m² (both by 24-hour continuous infusion), cisplatin 30 mg/m² repeated weekly.

Table 3. Toxicity

		Grade				
		0	1	2	3	4
Leukopenia	23	4	6	8	5	0
Granulocytopenia	23	7	3	7	6	0
Thrombocytopenia	23	18	2	2	1	0
Anaemia	23	12	0	7	4	0
Mucositis	23	20	1	2	0	0
Diarrhoea	23	18	3	2	0	0
Anorexia	23	18	3	2	0	0
Paresthesia	23	16	4	2	1	0
Hearing loss	23	20	1	2	0	0
Nausea	23	12	8	2	1	0
Vomiting	23	10	7	6	0	0

23 patients treated with 5-fluorouracil 1.2 g/m² and vinblastine 3 mg/m² both by 24-hour continuous influsion, and cisplatin 30 mg/m² repeated weekly.

DISCUSSION

Two related approaches to maximising the activity of standard chemotherapeutic drugs warrant further clinical investigation. One is to seek maximal dose intensity for single agents and combinations. This may be achieved either by tolerating more severe toxicity before dose modification, or by the concomitant use of agents that may rescue from the toxicity (e.g. colony stimulating factors); usually both strategies have been used

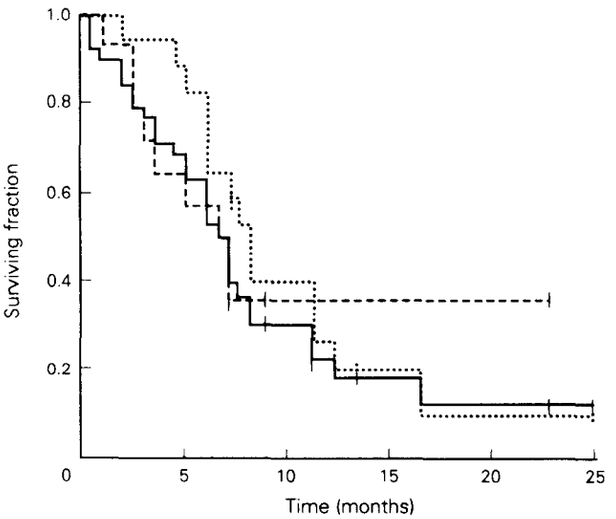

Fig. 1. Kaplan–Meier Survival curves for the whole group (– – –), responders (····) and non-responders (——). The three curves were not significantly different.

together. Historical analysis suggest the importance of this approach in several tumour types, though prospective validation is much-needed.

The second approach recognises that both the efficacy and the toxicity of antitumour drugs may be schedule-dependent. For some drugs (and some diseases) the standard short intensive course repeated at 3–4 week intervals may be inferior to alternative means of distributing the dose [7]. Response rates to some antimetabolites are higher on schedules of prolonged administration, while the activity of most alkylating agents is independent of the number of aliquots into which the total dose is divided. For some drugs, schedule manipulation may even provide a means to escalate dose intensity, since the reduced toxicity of divided doses may permit a higher total dose per course. Thus divided doses of cisplatin (100 mg/m^2 on days 1 and 8 of a 4-week course) yielded toxicity than that of the same total dose given over 4 days once per course [19]. The response rate to this regimen in NSCLC was 55% (in a cooperative group), a result comparable to the best combination regimens, though confirmation of these results is needed. Rusch *et al.* administered cisplatin 50 mg/m^2/week for 4 weeks to patients with mesothelioma, with comparable toxicity, and encouraging evidence of response [20].

In this study, cisplatin was administered at a dose intensity of 30 mg/m^2/week with tolerable toxicity. In addition, vinblastine and 5-fluorouracil were administered on a 24-hour infusion schedule repeated weekly. The dose intensity of vinblastine could not be increased by this strategy. This dose of 5-fluorouracil is substantially higher than that which would be tolerated by bolus administration. However, for cisplatin and vinblastine the dose intensity of this regimen is similar to that of a bolus regimen reported by Gralla *et al.* [1]. Therefore the study as designed is a reasonable test of the effect of schedule.

The response rate of 44% (95% confidence interval, 27–61%) in a patient population of which one-third had stage IIIB disease is encouraging in advanced NSCLC, and compares favourably to other single institution studies. Of great concern however, is the relatively short duration of response, and the minimal impact on survival. While comparisons of responders to non-responders have little meaning when the former outlive the latter, the failure to demonstrate such a difference must be viewed with concern. At a minimum, these results beg comparison with recent studies of 5-fluorouracil in colorectal cancer. When the drug is administered by prolonged continuous infusion, response rates of 40–60% have been reported [21]. Randomised studies confirm the higher response rates with infusional therapy, but demonstrate that these higher response rates fail to translate into improved survival [22].

In fact, these results are consistent with an analysis of various combination regimens and single agents in a large trial conducted by Bonomi for the Eastern Cooperative Oncology Group [23]. In this study, the objective response rates to the individual therapies were not reflected in the analysis of survival. The regimen with the highest response rate was associated with shorter survival than that observed following treatment with single agent carboplatin which had a response rate of only 9%. These findings suggest that re-evaluation of the relationship between response and survival in NSCLC is warranted. If survival is independent of the rate of objective tumor shrinkage, approaches to phase II evaluation of single agents and combination regimens may need to incorporate this endpoint.

On the other hand, the toxicity of this regimen (Tables 2 and 3) is such that further intensification of the dose of cisplatin may be possible. The results of Slevin and colleagues with prolonged oral administration of etoposide in small cell lung cancer should prompt an evaluation of this approach in NSCLC also. Finally, the availability of an active new agent (10-EDAM) may lead to the development of combination regimens with a greater long-term impact in this disease.

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Infusion of Floxuridine plus Etoposide plus Cisplatin in Human Malignancies

J. Lokich, C. Moore, N. Anderson and M. Bern

36 patients with advanced malignancy were studied in a phase I trial of continuous 24-h infusion of floxuridine (FUdR) plus etoposide plus cisplatin (FEP) administered for 5 consecutive days at 4-week intervals. Study design fixed the dose rate of etoposide and cisplatin with escalation of FUdR only. Dose rate-limiting toxicity related to the FUdR component was stomatitis and diarrhoea and was invariably associated with leukopenia and thrombocytopenia when grade 3 or 4 level gastrointestinal toxicity was observed. Only 3 of 64 courses were associated with transient renal failure related to cisplatin. Drug-related deaths occurred (leukopenia-associated sepsis) in 4 patients with poor performance status (ECOG 3 and 4). Responses occurred in 15 of 26 evaluable patients (all previously treated minimally or untreated) including 5/11 non-small cell lung cancer; 3/3 oesophageal; 2/2 breast; 4/5 gastric; 1 osteogenic sarcoma; and 1 unknown primary (probably ovary). The recommended dose rates for a 5-day infusion of the three agents for good risk patients is 20 mg/m² per day of each drug. For poor risk patients including age > 65 years; performance status 2 or greater; or extensive bone metastases or prior radiation; the recommended starting dose rates are: FUdR 15 mg/m² per day; etoposide 15 mg/m² per day; and cisplatin 20 mg/m² per day. Dose escalation of FUdR to a maximum of 25 mg/m² daily is feasible in selected patients demonstrating optimal tolerance.
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INTRODUCTION

ETOPOSIDE HAS been combined with platinum in an infusion for 24 h in two phase I trials which established the optimal dose rate for 3 [1] or 5 [2] day infusion of the two agents for a total dose of 150–225 mg/m² for etoposide and 90–100 mg/m² for platinum. The two drug combination has demonstrated synergism in experimental systems and, in addition, the mechanism of action of each of the drugs is distinctive; etoposide representing a plant alkaloid inhibits topoisomerase and platinum is a non-classical alkylating agent.

We undertook a phase I–II clinical trial adding a third agent in the form of a classical antimetabolite to the mixture. Floxuridine (FUdR) was selected on the basis of its established compatibility with platinum and a previous phase I trial in which floxuridine was admixed with platinum [3]. In addition, the initial two studies of the etoposide/platinum combination had demonstrated activity in gastric cancer a tumour for which the fluoropyrimidines in general and FUdR in particular has demonstrated some activity [4].

PATIENTS AND METHODS

Eligibility for entry into the clinical trial required an established histological diagnosis of advanced malignancy. The tumours must have had established resistance to standard therapeutic modalities or the malignancy was one for which no standard effective chemotherapeutic regimen existed. All patients must have had a life expectancy of at least 4 weeks to insure adequate evaluability. Additional prerequisites included: performance status by ECOG scale of 3 or less; white blood count of 3500/μl or more; platelet count of 125 000/μl or more; and creatinine clearance of greater than 50 ml/min. Patients must have completed at least a 4 week interval off chemotherapy if they had received prior chemotherapy of any kind and must have provided written informed consent as required by the Institutional Review Boards.

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