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Phase II Study of the Amsacrine Analogue CI-921 (NSC 343499) in Non-small Cell Lung Cancer

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CI-921 (NSC 343499; 9-[[2-methoxy-4-[(methylsulphonyl)amino]phenyl]amino] -N,5-dimethyl-4-acridinecarboxamide) is a topoisomerase II poison with high experimental antitumour activity. It was administered by 15 min infusion to 16 evaluable patients with non-small cell lung cancer (NSCLC) (7 with no prior treatment, 9 patients in relapse following surgery/radiotherapy) at a dose (648 mg/m^2 divided over 3 days, repeated every 3 weeks) determined by phase I trial. Patients had a median performance status of 1 (WHO), and median age of 61 years. The histology comprised squamous carcinoma (11), adenocarcinoma (1), mixed histology (2), bronchio-alveolar carcinoma (1) and large cell undifferentiated carcinoma (1). Neutropenia grade ≥ 3 was seen in 15 patients, infections with recovery in 3, and *grand mal* seizures in 1 patient. Grade ≤ 2 nausea and vomiting occurred in 66% courses and phlebitis in the infusion arm in 37%. 1 patient with squamous cell carcinoma achieved a partial response lasting 5 months. Further testing in this and other tumour types using multiple daily schedules is warranted.
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INTRODUCTION

CI-921 (NSC 343499; 9-[[2-methoxy-4-[(methylsulphonyl)amino] phenyl]amino] -N,5-dimethyl-4-acridinecarboxamide), a di-substituted derivative of the antileukaemic drug amsacrine, was developed in the Auckland Cancer Research Laboratory in an attempt to produce a drug with a spectrum of antitumour activity broader than that of the parent drug [1]. CI-921 has been found to act, like amsacrine, doxorubicin, etoposide and related compounds, on the enzyme topoisomerase II [2, 3]. CI-921 shows interesting *in vitro* properties in that it has similar toxicity to that of amsacrine against both mouse and human bone marrow cells, as measured by the drug sensitivity of colony-forming cells [4], but increased toxicity as compared to amsacrine against a variety of mouse and human tumour cell lines [4, 5]. This *in vitro* selectivity is mirrored *in vivo* by the greatly increased activity of CI-921 against experimental tumours such as P388 and L1210 leukaemia, Lewis lung adenocarcinoma and LC-12 lung squamous cell carcinoma [1, 6]. Pharmacological studies using advanced Lewis lung tumours have also shown that for a given plasma drug concentration, CI-921 is accumulated more effectively in solid Lewis lung tumours than is amsacrine [7].

Three phase I trials of CI-921 have been carried out, using a single dose schedule repeated every 3 weeks [8], a weekly dose schedule [9] and a daily schedule (for 3 days) repeated every 3 weeks [10]. The latter schedule, which identified a total dose of 648 mg/m^2 as optimal, has now been used for a limited phase II study of patients with non-small cell lung cancer. All patients had histologically-documented advanced disease which was inoperable, or which had recurred following surgery or radiotherapy. The aim of this study was to confirm the dose identified in the phase I study in a group of patients without previous chemotherapy, and to identify early disease activity in patients typical of future phase II studies.

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PATIENTS AND METHODS

Patient eligibility

Patients were required to have a performance status of ≤ 2 on the WHO scale (ambulant, capable of self care and less than 50% of daytime in bed) and be expected to survive more than 6 weeks. All patients had to have adequate pretreatment bone marrow function (absolute granulocyte count ≥ 1.5 × 10^9/l, platelets ≥ 100 × 10^9/l), liver function [alkaline phosphatase (ALP), aspartate transferase (AST), bilirubin ≤ 1.5 × upper limit of normal] and renal function (serum creatinine ≤ 0.13 mmol/l or ≤ 0.16 if creatinine clearance was > 1.0 m/s).

All patients were required to have measurable disease, demonstrated to be progressive over the 2 months prior to study, and could not have been previously treated with chemotherapy. Patients were ineligible if they had received radiotherapy in the 4 weeks prior to treatment with CI-921 (except small port radiotherapy to relieve symptoms) or major surgery within 14 days. Patients with a life-threatening illness unrelated to the tumour, serious infection within the prior month, or who required concurrent chemotherapy, radiotherapy or surgery were excluded.

Assessment of disease and toxicity

Pretreatment assessment in all patients included computed tomography of the chest and upper abdomen for accurate assessment of tumour size. Patients were fully restaged together with repeat computed tomography of the chest after two courses of treatment unless there was obvious disease progression clinically or on chest X-ray after the first cycle. Response was judged by standard WHO response criteria [11].

Treatment

CI-921, as the hydroxyethanesulphonate salt, was reconstituted in sterile water and diluted in 5% dextrose. From the phase I study a dose of 648 mg/m^2 (216 mg/m^2 daily for 3 days) was used, this being one dose step below the maximum tolerated dose [10]. If unacceptable toxicity occurred in the initial cycle, the dose in subsequent cycles was decreased by one step to 432 mg/m^2 (144 mg/m^2 daily for 3 days). It was planned to give the drug in 250 ml over 15 min on day 1, but in most patients pain at the site of infusion necessitated increasing the dilution to 500 ml with infusion over 30 min for subsequent treatments. Patients shown to have progressive disease discontinued treatment, while those with static disease or a disease response continued to a maximum of six courses.

RESULTS

Patients' characteristics

19 patients (3 females and 16 males) entered the phase II trial. 13 patients had squamous cell carcinoma, 2 had adenocarcinoma, 2 had mixed adenosquamous carcinoma, 1 had bronchio-alveolar carcinoma and one had undifferentiated large cell carcinoma. The median age was 61 (range 44–73 years). No patient had received prior chemotherapy. 9 patients had no prior treatment to the primary lesion although 3 had received cerebral irradiation for cerebral metastases and 1 had received local radiotherapy for painful bone metastases. 6 patients had relapsed following radiotherapy to the primary tumour, 2 patients following surgery and 2 patients following surgery and radiotherapy. At the time of entry into the trial, 1 patient had a performance status of zero, 17 patients of one and one of two. 41 treatment courses were completed and the median number of treatment courses completed per patient was two (range 1–6).

Response

16 patients were evaluable for response, having completed at least one 3-day treatment cycle. 1 patient with squamous cell lung cancer had a partial response after 2 treatment courses, with a decrease in size of a left upper lobe tumour mass from 6 × 5 cm to 3 × 3 cm. There as no further reduction in tumour size after 4 further cycles, but the response was maintained for 5 months before relapse. Progression of disease was apparent in 3 patients after the first cycle, 7 after the second, 2 after the third, 1 after the fourth and 2 after the fifth cycle. Whilst the 3 patients who received 4 or 5 cycles of CI-921 appeared to have stabilisation of disease for 3-4 months, none showed definite evidence of tumour shrinkage. All patients died with a median survival of 3.5 months from the start of treatment (range 1–27 months).

Toxicity

3 patients failed to complete the first 3-day treatment course, 1 because of intolerable discomfort in the back of the hand during drug infusion (with no pain thereafter and no extravasation or subsequent phlebitis), 1 because of rapid general deterioration clearly related to the disease rather than therapy, and 1 because of withdrawn consent. 13 patients received a second cycle, but 4 required dose reduction because of the degree of myelosuppression following the initial cycle (grade 4) and associated infection in 3 patients.

Haematological toxicity was assessed following 41 treatment courses (Table 1). Neutropenia (≥ grade 3) was seen in 26 courses (64%) and in at least one course in 15 patients. The median onset of neutropenia (≥ grade 1) was seen by day 8 (range 6–12) with recovery by day 18 (range 15–29). 3 patients developed a chest infection in association with neutropenia but all responded to antibiotics. A decrease in haemoglobin (≥ grade 1) was seen in 14 patients (50% of all courses) but was less than 3 g/l in all but 2 patients. A fall in haemoglobin (grade 2 and 3) was seen in 2 patients in association with severe infective illnesses. Thrombocytopenia occurred in only 1 patient who developed a grade 2 decrease in platelet count on day 13, with recovery by day 22.

Table 1. Haematological toxicity of CI-921

Grade	Neutrophils	Haemoglobin	Platelets
0	7 (0)	50 (2)	98 (15)
1	2 (0)	46 (12)	0 (0)
2	27 (1)	2 (1)	2 (1)
3	37 (7)	2 (1)	0 (0)
4	27 (8)	0 (0)	0 (0)

% of 41 treatment courses. Brackets indicate numbers of patients with worst toxicity of this level.

Non-haematological toxicity was generally mild (Table 2). Treatment was associated with nausea (grade 1) in 24 courses (59%) in 10 patients, and nausea and vomiting (grade 2) in 3 courses (7%) in 3 patients. The nausea was generally mild, associated with loss of appetite and resolved by day 4. Pain at the site of infusion led to the use of an increased infusion volume and slower infusion rates, but despite this, phlebitis was seen in 15 courses (37%) in 10 patients.

Abnormality of liver function tests occurred infrequently, and usually returned to normal within 4 days. 1 patient developed a

Table 2. Non-haematological toxicity of CI-921

Toxicity		Grade	No. (%) of courses	No. of patients with worst toxicity at this level
Nausea and vomiting		0	14 (34)	3
		1	24 (59)	10
		2	3 (7)	3
Phlebitis		0	26 (63)	6
		1	11 (27)	7
		2	4 (10)	3
Liver function	ALP	0	38 (93)	13
		1	2 (5)	2
		2	1 (2)	1
	AST	0	32 (78)	11
		1	7 (17)	4
		2	2 (5)	1
Renal function (serum creatinine)		0	39 (95)	14
		2	1 (2)	1
		4*	1 (2)	1
Infection		0	36 (88)	11
		1	1 (2)	1
		2	1 (2)	1
		3	1 (2)	1
		4	2 (5)	2
Seizures		3	3 (7)	1

* Probably related to study disease rather than study drug.

grade 1 increase in AST on day 4 in 4 of 5 treatment courses with return to normal levels by day 8. This was associated with a grade 1 elevation of ALP on one occasion only.

1 patient had mild impairment of renal function at the start of treatment (serum creatinine 0.16 mmol/l, serum urea 6.8 mmol/l) and developed severe renal dysfunction by day 10 of his first treatment course from which he subsequently died. *Post mortem* examination revealed extensive intra-abdominal disease surrounding the ureters bilaterally. Although it is not possible to exclude a contribution from CI-921, the renal impairment was thought to have resulted primarily from disease rather than the treatment. 1 other patient had a transient deterioration of renal function (grade 2 toxicity) in association with an infective episode.

Probable neurological toxicity was seen in 1 patient. This patient had a *grand mal* seizure temporally associated with CI-921 infusion in 3 of 4 cycles. The seizure occurred several hours after the third infusion in the first and second cycles, and after the second infusion on the fourth cycle. He was known to have a cerebral metastasis and had presented 5 weeks earlier with two *grand mal* seizures. Treatment with phenytoin was started at that time and no further seizures occurred until he commenced treatment with CI-921. He had received cerebral irradiation in the interim. His antiepileptic medication was changed from phenytoin to carbamazepine because of the development of an allergic skin rash during the first CI-921 treatment cycle. Carbamazepine concentrations within the therapeutic range were documented at the time of the second and third seizures, but the serum sodium was low (124– 126 mmol/l).During the third treatment cycle, when no seizure occurred, serum sodium did not fall below 128 mmol/l. The patient had no seizures between treatment courses and there were no other unexpected side-effects.

DISCUSSION

NSCLC is generally considered to be relatively resistant to chemotherapy, with low response rates to standard cytotoxic drugs. In this disease, even the single response in a group of 16 patients suggests that CI-921 in this administration schedule may have activity against NSCLC with a predicted true response rate of between $< 1\%$ and 30% (95% confidence limits). In a phase II study of the parent drug amsacrine in NSCLC [12] 3 partial responses amongst 76 patients were seen, giving a predicted true response rate of between $< 1\%$ and 11% (95% confidence limits). More patients are required to define the activity of CI-921 accurately and to distinguish it from that of amsacrine.

In another phase II trial of CI-921 against NSCLC in a 5-week course with drug administered on days 1, 8 and 15, only 1 of 31 evaluable patients with non-small cell lung cancer achieved a partial remission [13]. However, it is known that the schedule of administration may be vitally important to the activity of at least some topoisomerase II poisons. For example, in the much more chemosensitive small cell lung cancer, intermittent dosage schedules of etoposide are almost devoid of activity, whilst daily administration schedules over at least 5 days gives rise to response rates of up to 80% [14–16]. Moreover, experimental studies with CI-921 in the treatment of Lewis lung tumours in mice demonstrated the superiority of a multiple 12-hourly schedule (which in cytokinetic terms equates to the schedule used here) over single dose treatment [17].

Preliminary investigation has been made of CI-921 against other tumour types. In a multicentre phase II study [13] using the same intermittent schedule noted above (days 1, 8 and 15 of a 35-day cycle), two responses (1 complete response, 1 partial response) were noted in 17 patients with breast cancer. There was no response in colorectal cancer (19 patients) or gastric cancer (17 patients), but 1 partial response in each of head/neck and pancreatic cancer (13 patients each).

The spectrum and degree of toxicity seen with CI-921 was, in general, similar to that observed in the phase I study [10]. Myelosuppression was again the dose-limiting toxicity, with grade ≥ 3 neutropenia in 64% of treatment courses. It occurred at least once in 15 of the 16 patients. However, recovery from myelosuppression was rapid with a return to normal within a median of 10 days of the initial onset, suggesting that the correct dose for this schedule had been identified in the phase I study. Pain at the infusion site was common and necessitated an increased infusion volume and slower infusion rate. Despite this, mild phlebitis still occurred in over 50% of the patients. Phlebitis was an even greater problem in a study using a weekly schedule in which higher doses were administered [13].

The only additional possible toxicity identified in this study was the association of *grand mal* seizures with CI-921 infusion in 1 patient. The patient concerned had a cerebral metastasis previously treated by irradiation and had presented with seizures. This may well have been the basis for continuing epileptiform activity. On each occasion there was a co-existing factor that may have precipitated the seizure. This included a change of antiepileptic drugs on one occasion and mild hyponatraemia on 2 others. The seizures, which occurred despite therapeutic levels of carbamazepine on the last two occasions, happened only on treatment days and never between courses. It seems likely that the neurotoxicity of CI-921 may have been manifest only in the presence of an added trigger, such as hyponatraemia. In this way, the neurotoxicity of CI-921 may be analogous to the cardiotoxicity of amsacrine, where hypokalaemia appears to be a trigger [18].

In conclusion, the resistant nature of NSCLC to chemotherapy, with no drug currently in use providing response rates greater than 30% [19], implies that the finding of even a single response in a small group of patients warrants more testing. The responses noted in the small number of patients with other tumour types supports this conclusion. Etoposide, which has the same target of action as CI-921 in the cell, is effective against a range of clinical tumours including NSCLC, small cell lung cancer and breast and haematological malignancies. Further testing of CI-921 therefore seems warranted, either using the current schedule or exploring multiple daily schedules of longer duration.

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Phase II Intravenous Study of Epirubicin with 5-Fluorouracil in Patients with Advanced Hepatocellular Carcinoma

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Between August 1986 and September 1990, 22 previously untreated non-cirrhotic patients with measurable unresectable primary liver cancer were treated every 4 weeks with a combination of epirubicin and 5-fluorouracil. The dose of epirubicin was escalated; the starting dose was 40 mg/m^2, the second dose was 50 mg/m^2 and thereafter 60 mg/m^2 during subsequent cycles. The dose of 5-fluorouracil was always 800 mg/m^2. Objective response rate was 14%. Most of the patients experienced only mild haematological toxicity, and no other dose limiting toxicity was observed. Nonetheless, increasing the dose would probably not have increased the response rate.

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INTRODUCTION

MOST PATIENTS with advanced liver (hepatocellular) carcinoma fall within the sphere of palliative treatment and are therefore candidates for chemotherapy. The most effective single agents, doxorubicin and 5-fluorouracil, have at best yielded response rates of 25% among patients with hepatoma [1]. Epirubicin (4'epidoxorubicin) is an isomer of doxorubicin with a lower cardiotoxicity [2]. Systemic intravenous therapy with epirubicin has been tested in hepatocellular carcinoma. Two phase II studies have shown response rates of 9 and 17% [3, 4]. The aim of this study was to evaluate the efficacy and toxicity of epirubicin combined with 5-fluorouracil given intravenously in advanced inoperable or metastatic hepatocellular carcinoma.

Between August 1986 and September 1990, 22 consecutive, untreated non-cirrhotic patients with measurable and histologically and/or cytologically confirmed unresectable primary liver cancer were entered on the study. All histological and/or cytological specimens were re-examined. One of the tumours was fibrolamellar. The disease was confined to the liver in 14 patients (9 males and 5 females), whereas 8 patients (5 males and 3 females) were in the metastatic phase at presentation. The mean age of all patients was 51 years (range 16–69 years). The metastatic sites were distributed as follows: lung (2 patients), bone (3), distant lymph nodes (1) and peritoneal carcinosis (2).

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