Eur J Cancer Clin Oncol, Vol. 22, No. 4, pp. 435–437, 1986.
Printed in Great Britain.

0277-5379/86$3.00+0.00

A Phase II Study of Cyclophosphamide as a 24-hr Infusion in Advanced Non-Small Cell Lung Cancer

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Abstract—*Twenty patients with progressive non-small cell lung cancer who had received no prior chemotherapy were treated with* 24-hr *infusions of cyclophosphamide at a dose of* 2.5 g/m^2. *The median number of courses administered was three (range one to six). There was one PR and one CR, an overall response rate of* 10% (95% *confidence limits* 2–32%). *A further six patients experienced excellent relief of distressing symptoms, unresponsive to other measures, as a result of the chemotherapy. The median survival for the* 20 *patients was* 18.5 weeks (*range* 4–75 weeks). *The median leukocyte nadir count was* 1.1×10^9/l *and median platelet nadir count* 226×10^9/l. *There were no episodes of cystitis and gastrointestinal toxicity was moderate. This study has not shown any advantage for the infusion schedule over conventional bolus regimens, but further dose escalation or more prolonged infusion times may improve results.*

INTRODUCTION

CYCLOPHOSPHAMIDE used in an intermittent bolus schedule has been extensively tested in non-small cell lung cancer producing response rates ranging from 4 to 42% [1]. These studies suggest that a dose–response relationship exists, higher remission rates being obtained when doses of the order of 2–3 g/m^2 are used [2,3]. Recent work in mice by Klein *et al.* [4] has shown that higher doses of cyclophosphamide may be administered without additional toxicity by fractionating the dose over 24 hr. Moreover at equal dose levels there appeared to be an improved therapeutic effect for the 24-hr schedule. We therefore decided to test cyclophosphamide in a 24-hr infusion schedule in advanced non-small cell lung cancer.

PATIENTS AND METHODS

From January to October 1983 20 patients with a histologically confirmed diagnosis of non-small cell lung cancer were entered into the study. All patients had locally advanced or metastatic tumour with evidence of disease progression in the previous 4 weeks and symptoms that were not controlled by radiotherapy or simple palliative measures. Patient characteristics are shown in Table 1. Pre-treatment investigations included full blood count, biochemical profile, liver function tests and chest X-ray. Radioisotope and ultrasound scans were performed when clinically indicated.

A pilot study had shown that a dose of 2.5 g/m^2 administered over 24 hr every 21 days was well tolerated and produced acceptable haematological

Table 1.

Sex — Male	16
Female	4
Age in yr, median (range)	59 (36–72)
KP, median (range)	50% (40–70%)
Previous chemotherapy	0
Previous radiotherapy	8
Histology:	
Squamous cell	10
Adenocarcinoma	8
Large cell undifferentiated	2
Disease extent:	
Intrathoracic	12
Metastatic	8
Sites of metastases:	
Peripheral nodes	4
Liver (isotope scan)	1
Bone (isotope scan)	5
Soft tissue	3
Contralateral lung	3

Accepted 1 October 1985.
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toxicity. Cyclophosphamide was therefore administered as a 24-hr infusion at a dose of 2.5 g/m^2 in 4 × 500 ml N/saline with no additional hydration. Treatment was repeated every 21 days to a maximum of six courses. Patients were seen at 10–14 days following chemotherapy for assessment of haematological and other toxicity. Treatment was discontinued if there was evidence of disease progression after two courses and delayed by 1 week if full haematological recovery (wbc $> 3 \times 10^9$/l, platelets $> 100 \times 10^9$/l) had not occurred when retreatment was due. Treatment was also delayed, where appropriate, following episodes of infection.

Response was assessed by standard U.I.C.C. criteria [5].

RESULTS

The 20 patients received a total of 67 courses (median three, range one to six). Eighteen patients received two or more courses. The majority of patients experienced nausea with intermittent vomiting during the infusion which settled after 24–48 hr. Alopecia requiring a wig occurred in all cases but there were no episodes of cystitis. Myelosuppression was moderate, the median leukocyte nadir being 1.1×10^9/l (range $0.1–5.5 \times 10^9$/l) and median platelet nadir 226×10^9/l (range $30–885 \times 10^9$/l). Intravenous antibiotics were required on seven occasions for presumed septicaemic episodes in neutropaenic patients and oral antibiotics were used in a further seven cases for less serious infections. Nine patients were given blood transfusions when the haemoglobin fell below 8.5g/dl but no platelet transfusions were required. There were seven treatment delays, six due to intercurrent infection and one to persisting thrombocytopaenia.

There were two objective responses, one CR and one PR, an overall response rate of 10% (95% confidence limits 2–32%). Duration of response was 60 and 44 weeks respectively. In addition a further six patients experienced excellent relief of distressing symptoms, usually pain or breathlessness, as a result of the chemotherapy. The median survival was 18.5 weeks (range 4–75 weeks). There were no treatment-related deaths.

DISCUSSION

When used in conventional bolus schedules several of the available cytotoxic agents can produce responses and palliation in a proportion of patients with advanced non-small cell lung cancer [1]. However, little impact has been made on survival even with aggressive combination regimens [6–8]. Prolonged infusions may improve the therapeutic effect of these agents in several ways [9]. Tumour cells in resting phase may be recruited to active division during the infusion and thus exposed to drugs at the optimum time for cell kill. In addition intra-cellular drug levels may be increased if membrane transport is dependent on duration of exposure as well as peak drug concentration. The work of Klein *et al.* [3] suggested that fractionating the dose over 24 hr might improve the therapeutic ratio and anti-tumour effect of cyclophosphamide although the current study has not confirmed this. Despite 40% of patients benefiting from the chemotherapy in terms of symptomatic relief the objective response rate was only 10%. Moreover the median survival of 18.5 weeks did not differ from that in previous studies using similar doses of cyclophosphamide in bolus administration [2, 3]. This failure to show any advantage for the infusion schedule may be due to inadequate dosage which could be increased in view of the moderate toxicity in this study. Alternatively a longer infusion time might improve results particularly in tumours with lengthy cell cycle and slow tumour doubling times such as non-small cell lung cancer [10]. Technology now exists allowing prolonged infusions to be administered on an outpatient basis [11], making such schedules more acceptable to both patient and physician.

Approaches such as these must be investigated if progress is to be made in the common solid tumours.

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