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A Randomised Trial of Cyclophosphamide Pretreatment ('Priming') before Short-duration Chemotherapy for Small Cell Lung Carcinoma

STEPHEN HARLAND,* DAVID PEREZ,* JOHN MILLAR† and IAN SMITH*†
Lung Unit, Royal Marsden Hospital, Sutton, Surrey and §Institute of Cancer Research, Sutton, Surrey, U.K.

Abstract—*Forty-five patients with small cell anaplastic carcinoma of the bronchus were treated with four four-weekly courses of a combination of cyclophosphamide, vincristine and methotrexate. Randomisation was carried out to determine whether they received in addition* 1 g/m² *of cyclophosphamide* 1 week *before the three-drug therapy. Patients with limited disease received radiotherapy after their chemotherapy. Myelosuppression was similar in the two groups, but the additional cyclophosphamide did not improve remission duration or survival. Confining the chemotherapy to four courses did not give shorter survival times to those reported in other studies.*

INTRODUCTION

IT HAS been shown in mice that the administration of a small dose of cyclophosphamide several days before a large dose of the same drug or another alkylating agent significantly reduces toxicity to several normal tissues, including bone marrow, and increases survival [1, 2]. In man cyclophosphamide pretreatment ('priming') enhanced peripheral neutrophil recovery following high-dose melphalan [3]. Tumour growth delay studies using the murine FS6 sarcoma and human oat cell carcinoma xenografts grown in immune-deprived mice showed that priming did not protect the tumour from subsequent large doses of cyclophosphamide and, indeed, some degree of enhanced anti-tumour effect was obtained for the murine sarcoma and one of the two xenografts [4, 5].

In the trial reported here we have investigated whether this technique would allow significantly higher total doses of cyclophosphamide to be given safely to patients with small cell lung cancer with a consequent improvement in anti-tumour effect. Patients receiving short term (four courses) chemotherapy with a cyclophosphamide-containing regimen were therefore randomised to receive pretreatment cyclophosphamide or not before each course of therapy.

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MATERIALS AND METHODS

Forty-five previously untreated patients with small cell carcinoma of the lung were entered into the trial. Staging investigations included chest X-ray, serum liver function tests, bone marrow aspirate, isotopic bone scan and, where clinically indicated, isotopic liver scan. Patients were excluded from the trial if they were greater than 70 yr old or had CNS metastases at presentation.

Twenty-six patients had limited disease confined to one hemithorax, mediastinum, ipsilateral supraclavicular lymph nodes or ipsilateral pleural effusion. Further details of patient characteristics in both arms of the trial are given in Table 1.

Trial design and treatment

Trial design is shown in Fig. 1. All patients received combination chemotherapy using cyclophosphamide 1.5 g/m², methotrexate 30 mg/m²

Table 1. *Patient characteristics*

	Primed		Not primed	
	No.	%	No.	%
Total	20	100	25	100
Limited disease	11	55	15	60
Extensive disease	9	45	10	40
Male sex	10	50	15	60
Karnovsky >90	11	55	18	72
Mean age (yr)	59		61	
Age range (yr)	43-70		41-70	

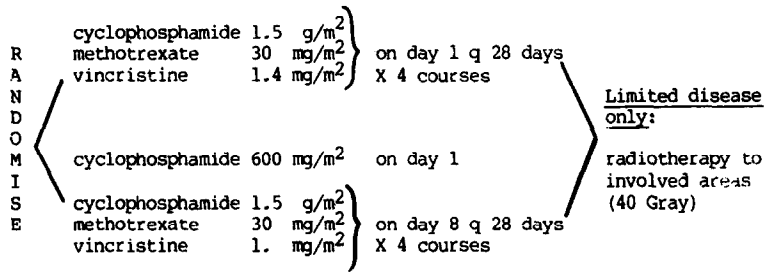

Fig. 1. Schema for chemotherapy in 'primed' and 'non-primed' arms of the trial.

and vincristine 1.4 mg/m² given by i.v. bolus injection once every 4 weeks for a maximum of four courses, or up to the time of disease progression. Before starting treatment patients were randomised to receive a pretreatment ('priming') dose of cyclophosphamide or not, given in a dose of 600 mg/m² by i.v. bolus injection 7 days before each course of treatment.

Patients with limited disease were given radiotherapy to the original site of intrathoracic disease to a total dose of 40 Gy in 20 fractions, after chemotherapy had been completed. No prophylactic cranial irradiation was given.

Response criteria

Complete remission was defined as disappearance of all clinical, biochemical and radiographic evidence of disease for a period of at least 2 months. Partial response was defined as a reduction in the product of two diameters of measurable disease by at least 50%.

RESULTS

Although stratification was not carried out before randomisation, no significant difference in any known factor which might influence the

Table 2. Response data

	Primed				Not primed			
	Total	PR	CR	PR + CR (%)	Total	PR	CR	PR + CR (%)
All patients	20	13	3	80	25	12	6	72
Limited disease	11	7	3	91	15	7	5	80
Extensive disease	9	6	0	67	10	5	1	60

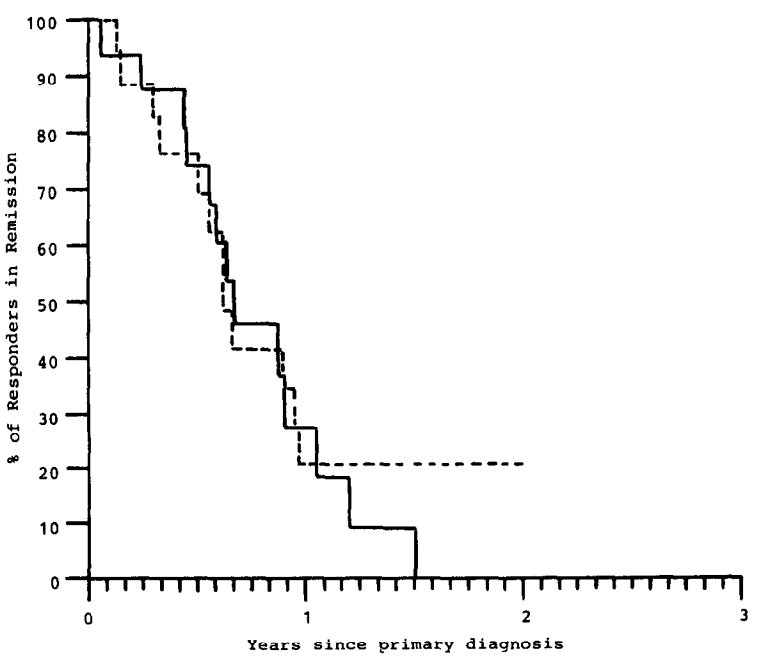

Fig. 2. Response duration. ———, primed patients; – – – –, non-primed patients.

prognosis emerged between the two groups (Table 1).

No significant difference in response rate was seen between the two groups of patients. Details of response in limited and extensive disease are given in Table 2. The median duration of response for 'primed' patients was 6 months, compared with 7 months for 'non-primed' patients (Fig. 2). The median duration of survival for 'primed' patients was 8 months, compared with 11 months for 'non-primed' patients (Fig. 3). These differences were not significant. Median survival for all patients with limited disease was 13 months and for extensive disease 7 months.

Peripheral leukocyte counts before and during the first two courses of chemotherapy for 'primed'

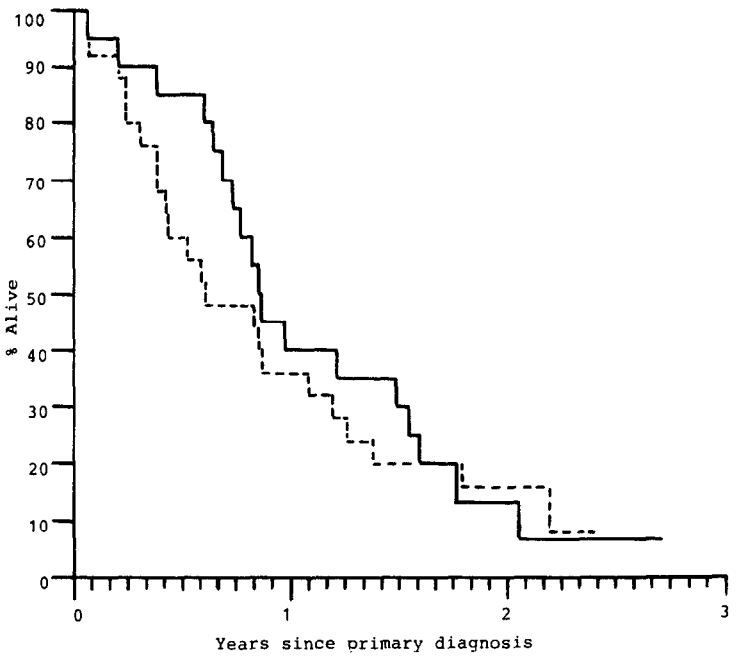

Fig. 3. Survival. ———, primed patients; – – – –, non-primed patients.

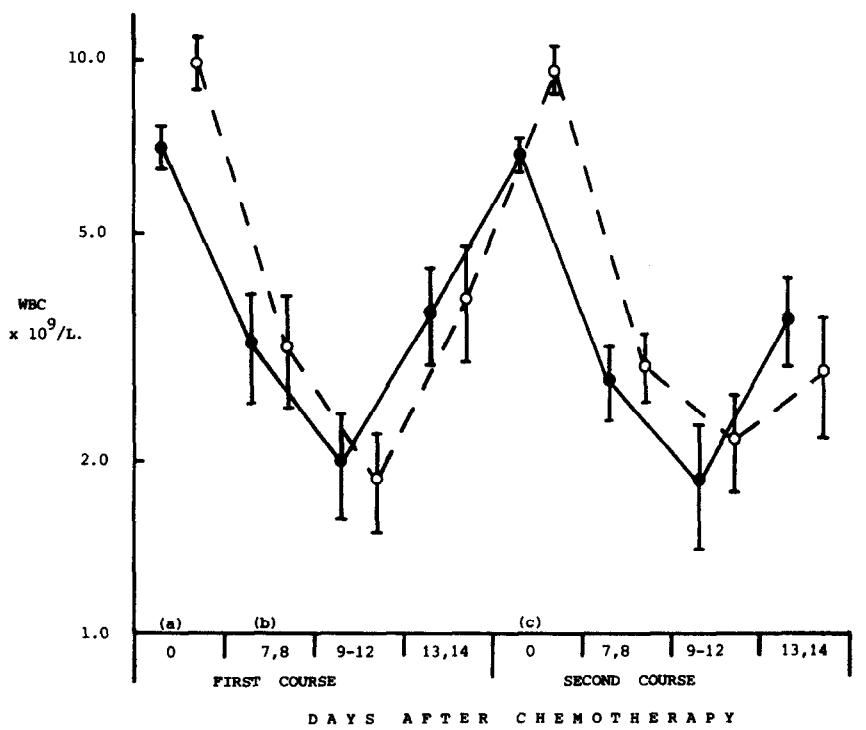

Fig. 4. Peripheral leukocyte count (± S.E.) following the first two courses of chemotherapy. Closed symbols, primed patients; open symbols, non-primed patients. NB Day 0 = the day of simultaneous treatment with vincristine, methotrexate and cyclophosphamide, for both groups. (a) P <0.05; (b) P >0.95; (c) P <0.01.

and 'non-primed' patients are given in Fig. 4. No significant differences were seen either in the nadirs or rates of recovery.

DISCUSSION

The exact mechanism underlying the cyclophosphamide 'priming' phenonemon is not fully understood. The rate of clearance of ^{14}C-labelled cyclophosphamide is not increased by a priming dose of the drug [5], so alteration of the pharmacokinetics is unlikely to be the explanation. It is known that priming causes some form of protection or enhanced recovery in several normal tissues [6]. In mice myelosuppression (which is not dose-limiting) is not reduced by priming, but recovery appears to be enhanced.

In this trial enhanced peripheral leukocyte recovery was not seen after a priming dose of cyclophosphamide, but it was nevertheless of interest that leukocyte recovery was just as rapid in the primed patients during the first two courses of treatment despite their having received 40% more cyclophosphamide than the non-primed controls. This observation suggests that cyclophosphamide priming might be used to increase the total dose of drug given without any concomitant increase in marrow toxicity.

Cyclophosphamide priming did not influence anti-tumour efficacy in terms of response rate, response duration or survival. This contrasts with experimental data in which an increase in tumour growth delay and cure was obtained with cyclophosphamide priming against the FS6 murine fibrosarcoma and one of two human oat cell xenografts [4, 5]. The inability to repeat this experimental effect clinically may not be surprising, however: low-dose chemotherapy is less effective than conventional-dose treatment [7], but several studies and trials have shown that moderate further increases in cyclophosphamide dosage (e.g. up to two-fold) are no more effective than conventional dosage but do result in increased toxicity [8–11].

Finally, it was of interest to us that the overall survival results in this trial after short-duration chemotherapy using only four courses of treatment were as good as those reported for most other studies using very much more protracted chemotherapy [12], suggesting that short-duration chemotherapy with its associated advantages may be as effective as much more prolonged treatment in the management of this disease.

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