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Clinical Trials Summaries

Phase II Study of 9-Hydroxy-2-methyl-ellipticinium Acetate (Ellipticinium) in Patients with Advanced Carcinoma of the Lung

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INTRODUCTION

THE ellipticine family are plant alkaloids most of which bind to DNA by intercalation.

Ellipticinium (9-hydroxy-2-methyl-ellipticinium acetate) is active in L1210 and P388 leukaemias, B16 melanoma and ependymoma in mice and Yoshida and Gardner lymphosarcomas in rats [2]. Trials in Europe have indicated anti-tumour activity in patients with breast cancer and occasional responses have been seen in squamous cell lung cancer, soft tissue sarcoma, Ewing sarcoma, neuroblastoma [3–5]. The principle toxicity of the drug consists of asthenia, dryness of the mouth, phlebitis, anorexia, nausea and vomiting, severe haemolysis after repeated exposure shown to be due to presence of IgM antibody and occasional nephrotoxicity [6].

The lack of myelosuppression and the lack of data in good performance status patients with lung cancer led to the following trial.

PATIENTS AND METHODS

All patients admitted to this EORTC trial were shown to have histological confirmation of metastatic lung cancer; measurable or evaluable disease, age of 70 or less, ECOG performance score 0 or 1, normal renal function, normal liver function tests and normal haematological parameters.

Ellipticinium was given by 90 min infusion at a dose of 100 mg/m^2 weekly, for 6 weeks and thereafter 2 weekly. Evaluation of response was planned after 6 weeks. The drug was mixed in 500 ml of 5% dextrose. Antibodies to the drug were checked before each injection starting after the 4th week. Histology was verified in all patients by a central panel of pathologists, and the study was designed to test the drug in 20 patients with each histological subtype.

RESULTS AND DISCUSSION

A total of 45 patients was entered into this study of whom three were ineligible due to a performance status higher than 1. Further, the response could not be evaluated in four patients who died within 6 weeks, two died after completion of the 2nd week of treatment, one refused after 1 week and one after 2 weeks. One partial response was seen in a patient with large cell carcinoma of the lung. This response was in lymph nodes and had a duration of 3 months. The disease progressed within 6 weeks in 25 patients and remained stable in 12. The median number of courses administered was four with a range of 1–9. More than half of the patients had not been pretreated with chemotherapy (Table 1) and the median performance score was 1. The reason for

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Table 1.

Total	
Entered	45
Eligible	42
Sex	
Male/female	37/5
Age (years) at entry	
Median	60
Range	46–70
Histological line	
Squamous	23
Adenocarcinoma	9
Large cell	5
Small cell	6
Histological grading (squamous and adenoca)	
Well differentiated	6
Moderately differentiated	6
Poorly differentiated	12
Unspecified	7
ECOG performance status	
Median	1
Range	(0–2)
Extent of disease	
Limited	11
Extensive	31
Prior therapy	
None	13
Radiotherapy	9
Chemotherapy	13
Radiotherapy + chemotherapy	7

patients not completing six weekly injections and indeed the reason for stopping the study before 20 evaluable patients had been treated in each cell type was the unacceptable nature of the toxicity encountered.

The treatment was stopped in 21 patients because of progression of the disease, in 14 patients due to toxicity. Six patients refused to continue and for one patient treatment was stopped after nine administrations without improvement of the disease.

Table 2. *Toxicity (WHO grades* 2–4)

Dry mouth	23
Nausea + vomiting	17
Phlebitis	9
Neurological	9
Drug fever	5
Diarrhoea	5
Haemolysis (reversible)	1
Leucopenia	1
Hypothermia (transient)	1

The most frequent toxicity observed (Table 2) was dryness of the mouth, which was reported in 31 patients (23 patients grade 2–3). Artificial saliva was used in 12 of these patients. The effect was disappointing with improvement in only five of them.

This schedule did not cause any significant nephrotoxicity but there was one episode of severe haemolysis (antibody positive) and one patient developed a transient hypothermic reaction, a side-effect not previously reported with ellipticinium.

CONCLUSION

Ellipticinium in this schedule gave disappointing anti-tumour effect and considerable non-haematological toxicity in this group of lung cancer patients with a good performance status.

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