recurrence in a 22-month-old girl [17]. Likewise complete tumour involution has been reported in a 21 year old female [18].

On this basis one might conjecture that at least part of the chemotherapy effect is attributable to a reduced ovary function. Ovarian suppression could therefore also be considered in the treatment of recurrent desmoid tumours. The unexpected tumour regression in one of our female patients following pelvic irradiation might be attributed to this effect.

In summary, our data are in agreement with the recent literature and support a policy of postoperative radiotherapy with 60 Gy in established cases of incomplete excision or gross residual disease following surgery. A policy of watchful expectancy might be considered in young patients with minimally positive or uncertain margins where it is assured that any recurrence will be readily resectable.

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Eur J Cancer, Vol. 28A, No. 4/5, pp. 835–837, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Chronic Oral Etoposide in Non-small Cell Lung Carcinoma

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25 consecutive inoperable or extended non-small cell lung cancer (NSCLC) patients (19 non-chemotherapy pretreated, 6 non-heavily pretreated) were given oral etoposide, 50 mg/m²/day for 21 successive days, every 4 weeks. 5 partial responses (PR), 9 disease stabilisations were achieved; the overall response rate of 20% (95% confidence interval, 4% to 36%) or 26% in non-pretreated patients. Median survival and PR duration probabilities were 6.7 months and 6.3 months, respectively. Alopecia excepted (96% of patients), non-haematological toxicity was mild. Haematological toxicity WHO grade II+III mainly consisted of leukopenia (28%).
Eur J Cancer, Vol. 28A, No. 4/5, pp. 835–837, 1992.

INTRODUCTION

ETOPOSIDE IS a schedule-dependent drug in preclinical systems [1] and in human oncology [2]. In small cell lung cancer (SCLC) the etoposide 5-day schedule has achieved a higher survival rate than the 1-day course [3]. The 8-day schedule has shown similar rate and duration of responses but lower toxicity than the 5-day course [4]. Based on the etoposide mechanism of action, preclinical studies and clinical data, Greco *et al.* started clinical research of a new schedule they called "chronic oral etoposide", in which etoposide is given orally for 21 consecutive days [5]. This new schedule has given promising results in SCLC, germ-cell tumours and non-Hodgkin lymphomas [6, 7]. The present study describes our experience with chronic daily oral etoposide in the treatment of advanced non-small cell lung cancer (NSCLC).

PATIENTS AND METHODS

25 consecutive NSCLC patients were entered into this trial from March to November 1990. Eligibility criteria were age,

40–80 years; histological diagnosis of NSCLC; inoperable or extended disease; ECOG performance status 0 and 1 (only those patients with >5% weight loss during last 6 months; other patients with <5% weight loss were included in another trial), 2 and 3 (all patients); evaluable or measurable disease; no previous chemotherapy (19 patients) or non heavily pretreated patients (no more than 3 courses of the same conventional chemotherapy completed at least 4 weeks before starting etoposide, 6 patients); haemoglobin levels of at least 10 g/l, white blood cell counts $>4 \times 10^9$/l and a granulocyte count $>2 \times 10^9$/l, a platelet count above 130×10^9/l; serum creatinine < 1.4 mg/dl and serum bilirubin < 1.5 mg/dl; life expectancy > 3 months.

Pretreatment evaluation included history and physical examination, complete blood cell (CBC) count, laboratory values for kidney and liver, posterior and lateral chest X-ray examination, thoracic computed tomography and other appropriate examinations were performed based on symptoms. CBC counts were repeated on day 14 of the first course and subsequently before and after each treatment subsequently. Liver and kidney chemistries were performed every 3 weeks.

The starting dose was 50 mg/m^2, daily for 21 consecutive days, two cycles before response evaluation. At the end of each cycle a rest period of 8 days was mandatory.

Non-responding patients after two cycles were excluded from this study. Responding and stable disease patients were given etoposide courses until tumour progression or excessive toxicity, with a maximum of six cycles per patient. Patients were supplied with oral etoposide, 50 mg soft gelatine capsules. In the day-hospital they were told about the probable main secondary effects, dosage, schedule (daily capsules were to be taken all at once, at least 3 h after dinner), and warned against stopping chemotherapy without contacting us personally or by phone. Metoclopramide (10 mg, orally, every 6–8 h) was prescribed to patients, but they were told about using it only if suffering from nausea and vomiting.

Since oral etoposide is supplied in 50 mg capsules, a daily dose of 50 mg/m^2 is reached over 2–3 days dose adjustments in which depending on patient body surface the daily dose should be one or two capsules. For instance, 80 mg being the daily dose for a patient with a body surface of 1.62 m^2, the drug was administered at 100, 100 and 50 mg on 3 consecutive days and this schedule was repeated for 21 days (median daily dose: 83 mg). Each patient was provided with a calendar in which the daily number of capsule intake was stipulated.

Depending on the haematological profile variations, etoposide was interrupted if leucocyte count was below 2×10^9/l and/or granulocyte count 1×10^9/l and/or platelet count 7×10^9/l. After haematological recovery (at least a leucocyte count $>3 \times 10^9$/l, a granulocyte count $>1.5 \times 10^9$/l and a platelet count $>100 \times 10^9$/l), chemotherapy dosage was cautiously reduced by 25% in subsequent courses.

Chest X-ray examinations were repeated after two cycles in all patients and thoracic computed tomography in responding patients. Predominant metastatic site appropriate examinations were performed periodically, but after at least two courses.

WHO criteria [8] were used for tumour response and toxicity evaluation. Survival and response durations were plotted according to the Kaplan–Meier method. Survival was calculated from the etoposide starting day and duration of response from the first day a remission was documented to the day progressive disease was first noted. Contingency tables were used in comparing proportions. Confidence intervals were calculated according to Simon [9]. In Table 1 are the main characteristics of the patients.

Table 1. Chronic oral etoposide in NSCLC (n = 25)

Patients' characteristics	
Median age in years (range):	59 (41–76)
Male/female:	20/5
Median performance status (range):	2 (0–3)
	No. of patients
Adenocarcinoma	9
Squamous cell carcinoma	11
Large cell carcinoma	3
Non small cell carcinoma*	2
Stage II†	3
Stage III B	7
Stage IV	15
Prior chemotherapy	6

*NSCC: Agreement was not reached by the reviewers in allocating these two cases to the major NSCC subtypes.
†They were included because previous ventilatory exams precluded them from surgery.

RESULTS

Response and survival

The 25 patients included were fully evaluable. 5 of the 25 patients had partial response (PR); 9 stabilisation and 11 progression (Table 2). The overall rate of response was 20%, 5 PR out of 25 patients (95% confidence interval, 4–36%) or 26% in non previous chemotherapy treated patients (5 PR out of 19 patients).

With a maximum follow-up of 311 days the 5 responders are alive and continuing in PR (median duration 88 days; range 85–183 days); median survival of the 25 evaluable patients was 122 days (range 64–311 days).

Toxicity

Chemotherapy course average per patient was 2.5 (range 1–6). In 56 out of 64 courses (87%) patients took the scheduled dosage

Table 2. Toxicity of oral etoposide in NSCLC

	Grade*			
	0	I	II	III
Haemoglobin	12†	8	3	2
Leucocytes	14	4	7	0
Granulocytes	16	6	2	1
Platelets	24	1	0	0
Nausea/vomiting	8	8	6	3
Diarrhoea	17	5	2	1
Mucositis	21	1	3	0
Alopecia	1	1	13	7

*World Health Organization.
†No. of patients.

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Revised 9 Sep. 1991; accepted 27 Sep. 1991.

(50 mg/m^2, 21 consecutive days) while the remaining 8 courses (7 due to haematological toxicity, 1 because of diarrhoea) were reduced by 25% of the initial dose.

The predominant picture of toxicity (Table 3) consisted of anaemia, leukopenia, nausea–vomiting and alopecia. No grade IV toxicity was observed. No etoposide toxicity related deaths occurred.

Previously chemotherapy treated patients (6 out of 25) showed non significantly ($P = 0.078$) worse haematological toxicity compared with patients (19 out of 25) without previous chemotherapy.

DISCUSSION

Etoposide is a phase-specific semi-synthetic podophyllotoxin derivative active in various solid tumours and malignant haemopathies [10]. Its remarkable schedule dependency; 50% (range, 25–75%) oral bioavailability; both intravenous and oral clinical activity; foreseeable and generally reversible toxicity, several drugs (cyclophosphamide, platinum, etc) synergism, are among the main features of this drug [10–12]. It seems that the chronic oral etoposide schedule has pointed to wider activity possibilities [2, 5–7].

In NSCLC, etoposide single agent response rate is approximately 10% [13, 14]. Without trying to compare results from independent pilot studies the 20% response rate observed in this trial (26% in non previous chemotherapy treated patients) suggests that this drug could be more active in NSCLC than former etoposide schedules indicated.

As in our previous trials with oral etoposide [15–18], patients were recommended to take the capsules late at night, although according to Harvey *et al.* [19] etoposide absorption is not altered by food.

Alopecia excepted, non-haematological toxicity was mild. Since our patients did not have serum etoposide levels measured, the high rate (96%) of alopecia in different grades reassured us about patients home drug compliance. Nevertheless, pharmacokinetic monitoring should be advised. Haematological tolerance was good with reversible toxicity. Neither leukopenia nor granulocytopenia, both life-threatening were detected. Packed red blood cell transfusions were needed for only 2 patients. This picture of high tolerance coincides largely with the expected toxicity for this set of mainly non-pretreated patients (19 out of 25), but without significant differences between pretreated (none of them heavily pretreated, as can be seen in Table 1) and no treated patients in this trial.

Although oral etoposide in this study showed interesting activity and mild toxicity mainly in non previously treated NSCLC patients, no definite conclusion of its superiority over standard intravenous schedules can be drawn. Further evaluation of this schedule is warranted.

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