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Treatment of Extensive Small Cell Lung Cancer with Carboplatin and Teniposide

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The combination of carboplatin and teniposide has been evaluated in a phase II trial including 47 previously untreated patients with extensive small cell lung cancer. Treatment was given at monthly intervals at a dose of 200 mg/m² of carboplatin intravenously on day 1 and teniposide at a daily dose of 60 mg/m² intravenously on days 1–5. Treatment response was complete in 4 (8.9%) and partial in 19 (42.2%) of 45 evaluable patients. The overall response rate was 51.1% (95% confidence interval 36%–66%). The median duration of response was 7.1 months (range 2.1–14.8) and the median survival was 6.7 months (0.3–22.2). Myelosuppression was the most prominent side-effect. Leukopenia (WHO grade 3–4) developed in 17 (37.8%) and thrombocytopenia (grade 3–4) in 5 (11.1%) of 45 patients evaluable for toxicity. 2 treatment-related deaths were registered. The present study shows that the combination of carboplatin and teniposide produces an acceptable response rate, but response duration and survival time are short.
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INTRODUCTION

SMALL CELL LUNG CANCER (SCLC) has a very high mortality and patients with extensive disease cannot at present be offered treatment with a curative intent. However, the tumour does respond to several cytostatics and different chemotherapeutic regimens have produced high response rates. The combination of cisplatin and etoposide has been especially promising with reported response rates of up to 88% in patients with extensive SCLC [1, 2].

The second generation platinum analogue carboplatin also appears to be effective. Smith *et al.* [3] reported an overall response rate of 60% in 9 patients with limited disease and 21 patients with extensive disease. Carboplatin was given as a single agent at a dose of 300–400 mg/m². Myelotoxicity, especially thrombocytopenia, was a dose-limiting factor in this treatment.

The podophyllin derivative teniposide has an effect which seems equal to or even better than that of etoposide. Thus Bork *et al.* [4] found a 90% response rate in SCLC patients treated with teniposide as a single agent, 60 mg/m² daily for 5 days every third week. Leukopenia was a dose-limiting factor, but thrombocytopenia was mild and transient.

These studies suggest that the combination of carboplatin and teniposide may have a chemotherapeutic potential that matches that of cisplatin and etoposide. A major advantage of carboplatin over cisplatin is the absence of nephrotoxicity and neurotoxicity which opens the prospect of an improved therapeutic ratio.

In February 1986, a dose escalation study was started with the purpose of finding a safe dose level for the combination of carboplatin and teniposide in the treatment of patients with extensive SCLC. The first 3 patients were treated with carboplatin 200 mg/m² day 1 and teniposide 60 mg/m² days 1–5 every fourth week. None of these patients incurred any serious toxicities. The next 3 patients had a higher dose of carboplatin, 250 mg/m², while the dose of teniposide was held constant. One of the patients treated with carboplatin 250 mg/m² died of sepsis with serious bone marrow depression 2 weeks after the start of treatment.

The dose escalation study was therefore stopped and the study was continued as a phase II study with the aim of evaluating the response rate and toxicity of the combination of carboplatin and teniposide given to patients with extensive SCLC.

PATIENTS AND METHODS

The study included 47 previously untreated patients with cytologically or histologically verified SCLC. 3 of the patients were patients from the phase I study, treated with the same carboplatin and teniposide doses as was prescribed for the phase II study. Eligibility criteria were: age $\leq$ 70 years, measurable disease, performance status (WHO) $\leq$ 3, leucocyte count $\geq 3 \times 10^9$/l, thrombocyte count $\geq 100 \times 10^9$/l and normal renal function (serum creatinine $<$ 110 μmol/l). Furthermore, all patients had extensive disease according to standard staging criteria [5]. Staging was based on the following pretreatment examinations: chest X-ray, physical examination, ultrasound examination of abdomen, bone scan and bone marrow aspiration. Patients treated with radiotherapy against the primary tumour before start of chemotherapy were excluded.

Some patient characteristics are summarised in Table 1.

Carboplatin was administered on day 1 at a dose of 200 mg/m². Teniposide was given on days 1–5 at a daily dose of 60 mg/m². Both drugs were given as intravenous infusions over 30–60 min. Leucocyte and thrombocyte counts were performed every week between the courses. Creatinine clearance based on 24-h urine collection was measured before each course. The treatment was repeated every fourth week. If there was evidence for progressive disease, the treatment was stopped. After 6 courses the treatment was stopped if the patient had no change or complete response. If the patient had partial response after 6 courses, the treatment could be continued with a palliative intend (maximum 9 courses).

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Table 1. Patients' characteristics

Total no. of patients	47
Evaluable for response	45
Evaluable for toxicity	45
Age	
Median	58.4
Range	(40.7–69.3)
Men/women	27/20
Performance status (WHO)	
0	2
1	13
2	20
3	12
Distant metastatic site*	
Bone marrow	6
Liver	22
Central nervous system	0
Bones	11
Suprarenal glands	5
Pleura	14
Lung	3
Lymph-nodes	6
Other	5

*29 patients had known metastases in one and 18 patients in two or more organ sites.

The dose of both drugs was reduced by 10% in case of leucocyte nadir 2.0–2.9 $\times$ 10^9/l or thrombocyte nadir 50–74 $\times$ 10^9/l. For leucocyte nadir 1.0–1.9 $\times$ 10^9/l or thrombocyte nadir 25–49 $\times$ 10^9/l, the doses were reduced by 25% and by 50% if leucocyte nadir was $< 1.0 \times 10^9$/l or thrombocyte nadir $< 25 \times 10^9$/l.

Evaluation of toxicity was based on weekly blood counts. A minimum requirement was that the counts from the first treatment cycle were available.

Response was evaluated according to WHO criteria [6]. All patients were evaluated by external review. For complete and partial responders, duration of response was calculated as the period from the first day of treatment to the day when progressive disease was first observed.

RESULTS

47 patients were included in the study. The patients received between 1 and 9 courses (mean 4.5). 8 of the patients only received one treatment course; 2 patients died due to progressive disease, 2 died due to treatment complications, 1 patient changed to other treatment because of rapid progression and 1 patient refused further treatment.

Table 2. Response to treatment with carboplatin and teniposide

Treatment courses	
Median	4.5
Range	(1–9)
Response %	
CR	4 (8.9)
PR	19 (42.2)
Duration of response (mo)	
Median	7.1
Range	2.1–14.8

CR = complete response and PR = partial response.

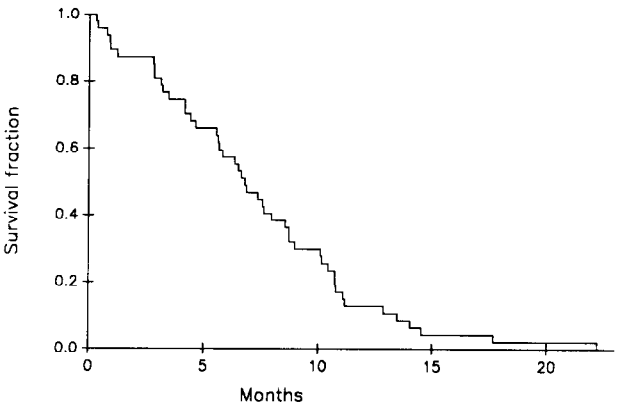

Fig. 1. Crude survival after start of treatment. All 47 patients are included.

Response was evaluated in 45 of 47 patients; 2 had died from treatment complications before the second course and thus they were not evaluable for response.

Complete response (CR) was achieved in 4 (8.9%) and partial response (PR) in 19 (42.2%) of the 45 patients. The overall response rate was 51.1%, (95% confidence interval 36%–66%). The median duration of response was 7.1 months (range 2.1–14.8 months). Details are shown in Table 2.

The median survival time for all the 47 patients from the first treatment with carboplatin and teniposide was 6.7 months (range 0.3–22.2 months). Survival is shown in Fig. 1.

Toxicity was evaluable in 45 of the 47 patients; 2 had died within the first month and without weekly blood counts the patients were not eligible for toxicity assessment. The 2 deaths appeared to be unrelated to chemotherapy administration. Necropsy in both cases indicated that widespread disease was the primary cause of death.

Myelosuppression in the form of leukopenia was the major dose-limiting side-effect. 17 patients (37.8%) had leukopenia WHO grade 3 or 4, whereas 5 patients (11.1%) had thrombocytopenia WHO grade 3 or 4. Details are shown in Table 3. In spite of this myelosuppression, subsequent treatment had to be delayed because of infection or myelotoxicity in only 4 cases. Dose reductions were not more frequently needed with increasing course number, and thus there were no evidence for cumulative toxicity. Details are shown in Table 4. Infections associated with leukopenia were observed in 9 cases, 4 were minor and 5 were moderate or severe infections. There were 2 treatment-related deaths within the first month. Both patients developed pneumonia in association with leukopenia and died 9 and 21 days after the first course, respectively.

Platelet transfusion was required in 2 of the 5 with thrombocytopenia. Alopecia grade 3 was seen in almost all patients. Nausea and vomiting were generally mild and easily treated with antiemetics.

We measured creatinine clearance and serum creatinine before every course. In Fig. 2, clearance values of 5 typical patients are shown. As appears from the figure, repeated creatinine clearance measurements showed considerable intra-individual variation. All measured serum creatinine values were within the normal range and none of the patients showed a more than 25% increase in serum creatinine from pretreatment measurement to measurement after their last course.

Table 3. Blood count nadirs after carboplatin and teniposide in patients evaluable for myelotoxicity

WHO grade	Patients *n* (%)
Leucocyte count	
0	7 (15.6)
1	5 (11.1)
2	16 (35.5)
3	10 (22.2)
4	7 (15.6)
Thrombocyte count	
0	35 (77.8)
1	1 (2.2)
2	4 (8.9)
3	2 (4.4)
4	3 (6.7)
Haemoglobin	
0	24 (53.3)
1	14 (31.1)
2	7 (15.6)
3	0
4	0

Data represent worst toxicity for each patient throughout all treatment courses.

DISCUSSION

The combined regimen of carboplatin and teniposide produced a 51% response rate which is close to that found by Smith *et al.* [3] for treatment with carboplatin as a single agent in previously untreated patients with extensive SCLC.

The study reported by Bork *et al.* [4] for teniposide given as a single agent to patients with previously untreated SCLC showed a higher response rate of 90%. Bork's study included only patients with WHO performance status ≤ 2 and 64% of the patients had limited disease. Performance status and disease stage are very important prognostic factors in SCLC and a comparison of the teniposide study and our study is difficult as the selection criteria were different.

In a phase II trial, combined cisplatin and etoposide produced a response in 15 of 17 (88%) patients with extensive SCLC [1]. The median survival of 9.8 months was comparable to 6.7 months in the present study.

Smith *et al.* [7] have described the effect of carboplatin

Table 4. Dose reductions

Course no.	No. of patients	Dose reductions *n*	(%)
1	47	–	–
2	39	28	29.2
3	35	25	28.6
4	30	21	30.0
5	24	17	29.2
6	21	12	42.9
7	8	6	25.0
8	5	4	20.0
9	3	3	0.0

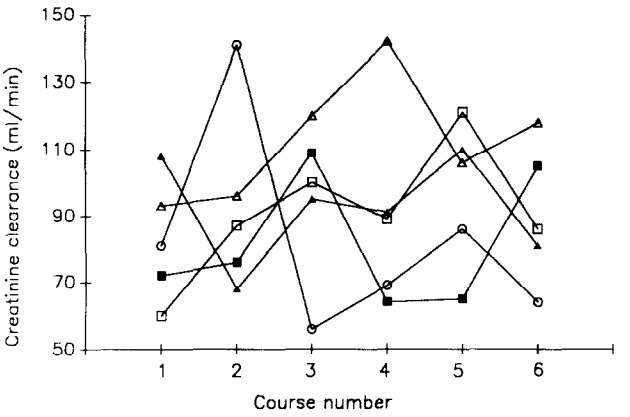

Fig. 2. Creatinine clearance estimated before courses 1–6 in 5 typical patients.

300 mg/m^2, day 1 and etoposide 100 mg/m^2, days 1–3 given every 4 weeks. Response was found in 88% and the median survival was 9.5 months among 24 patients with extensive disease.

Bishop *et al.* [8] treated 58 patients with extensive SCLC with carboplatin 100 mg/m^2, days 1–3 and etoposide 120 mg/m^2, days 1–3. They found an overall response rate of 58% and a median survival of 8.2 months.

Evans *et al.* [9] treated 34 patients with extensive SCLC with the same schedule of carboplatin and etoposide as Smith *et al.* [7] and they found response in 56% and a median survival of 8.7 months.

The mean response rate for patients with extensive disease calculated from these three reports of treatment with carboplatin and etoposide [7–9] was 64% which is only marginally different from our results.

Only one centre has reported results on treatment with the combination of teniposide and carboplatin in SCLC patients. In 1989, Goss *et al.* [10] described the preliminary results of a phase II study of teniposide 60 mg/m^2, days 1–5 and carboplatin 400 mg/m^2, day 1, given every 28 days. This schedule is very similar to the one we used except that their carboplatin dose was twice as high as ours. Goss *et al.* [10] obtained complete response in 1 (9%) and partial response in 8 (73%) out of 11 patients with extensive disease.

In spite of the lower carboplatin dose used, we have seen 2 treatment-related deaths caused by myelotoxicity in the present study and 1 treatment-related death in the previous phase I study. This unexpected myelotoxicity may stem from an impairment of the renal function which is reported to be associated with carboplatin retention and thus increased risk of myelosuppression [11, 12]. Perhaps a better effect of the combination of carboplatin and teniposide can be obtained with higher doses of the cytostatics. However, we must warn against an indiscriminate dose increase because treatment-related deaths occurred even with the rather low treatment dose used in the present study. The carboplatin dose can probably be calculated in a biologically more correct way by tailoring the dose to the glomerular filtration rate (GFR) instead of the patient surface area as proposed by Calvert [13]. This method seems to allow a safer administration of an increased dose intensity.

To register any nephrotoxicity in the present study, GFR was measured before each course by creatinine clearance. The obtained creatinine clearance values increase and decrease, apparently at random. In our opinion these measurements were

unreliable for the estimation of GFR. The patients most often collected the 24 hour urine on an outpatient basis, and we believe that these unsatisfactory results can be caused by imprecise urine collection.

It is evident from the present study and the above mentioned reports that the combination regimens of platinum and podophyllin derivatives can produce high response rates in the treatment of extensive SCLC, but it is rather disappointing that response duration and survival time remain very short. A possible step forward could be dose intensification combined with haematopoietic growth factors.

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Ifosfamide in Advanced Adenocarcinoma of the Oesophagus or Oesophageal–Gastric Junction Area

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25 previously untreated patients with inoperable or metastatic adenocarcinoma of the oesophagus or oesophageal–gastric junction area were treated with ifosfamide 6 g/m² over 48 hours, combined with mesna 6 g/m². 1 complete response and 1 partial response were seen among 23 patients evaluable, with a response duration of 29+ months and 7 months, respectively. Toxicity was not severe: grade 3 infection in 2 patients, grade 3 leucopenia in 3 patients and grade 3 nausea in 4 patients. No life-threatening episodes or central nervous system toxicity were encountered. Ifosfamide has limited activity in adenocarcinoma of the oesophageal–gastric junction area.

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INTRODUCTION

THE OUTLOOK for patients with adenocarcinoma of the oesophagus is dismal; in about 40% metastatic disease is apparent at first presentation. Even if a patient is operable, the 5-year survival after surgery with curative intent is < 10%. Most of these patients die with distant metastases. Obviously, there is a need for effective chemotherapy. We investigated the activity and toxicity of ifosfamide.

PATIENTS AND METHODS

Until July 1990, 25 consecutive previously untreated patients were entered in the study. The main eligibility criteria were histologically proven adenocarcinoma of the oesophagus or oesophageal–gastric junction area, with or without Barrett's epithelium (patients with adenocarcinoma of the gastric cardia, without involvement of the oesophageal–gastric junction area were not eligible); performance status (Karnofsky) > 60% and