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Is Carboplatin and Oral Etoposide an Effective and Feasible Regimen in Patients with Small Cell Lung Cancer?

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The combination of carboplatin and etoposide is an active and well-tolerated regimen in the treatment of small cell lung cancer (SCLC). The aim of the study was to confirm whether the efficacy could be maintained if etoposide was administered orally. 106 consecutive, unselected, and untreated patients with SCLC (limited disease (LD) 44; extensive disease (ED) 62) were treated with a combination of carboplatin 300 mg/m^2 intravenously (i.v.) day 1 and etoposide 240 mg/m^2 orally days 1–3 every 4 weeks for six courses or until progression. If oral treatment was inconvenient, i.v. etoposide (120 mg/m^2 days 1–3) was allowed. Thoracic irradiation (45 Gy in 22 fractions, split course) was given after three courses of chemotherapy to 29 patients with LD. Objective response (complete and partial) was seen in 89% (confidence interval (CI) 75–97) of patients with LD and in 53% (CI 40–66) with ED. Complete response was seen in 41% (CI 26–57) of patients with LD and in 8% (CI 2–18) with ED. Median time to progression for responders was 11 months and 6 months for patients with LD and ED, respectively. Corresponding median survival was 15 months (range 1–45 months) and 8.5 months (0–26 months). Myelosuppression comprised the main toxicity. Leucopenia (WHO III-IV) was observed in 20% and thrombocytopenia (WHO III–IV) in 16% of the cases. One patient died of sepsis during leucopenia. Oral treatment was convenient for most patients and therapy well tolerated. However, 9 patients (20%; CI 9–36%) with LD and 26 patients (42%; CI 29–56%) with ED received at least part of the etoposide treatment i.v.. The present study shows that the combination of carboplatin and oral etoposide is active and well tolerated, and may be used on an outpatient basis in patients with small cell lung cancer.

Key words: small cell lung cancer, chemotherapy, carboplatin, etoposide, oral therapy
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INTRODUCTION

FOR THE last two decades, cytotoxic therapy has been the principal treatment of patients with small cell lung cancer (SCLC) [1]. Objective responses have been recorded in more than 80% of patients using combination chemotherapy [1,2]. In previously untreated patients, cytotoxic therapy has increased median survival 5-fold, with long-term survival in 5–10% of the group as a whole [1–3]. However, it remains an unfortunate reality that many patients relapse within a short time after therapy, and the majority of patients die within the first 2 years [2, 3].

Various combinations of two to five active agents have been tried. No standard cytotoxic therapy exists [1], but the combination of cisplatin/etoposide or the addition of etoposide to well-known combinations seem superior to other regimens [2, 4–7]. Carboplatin–etoposide is an active, well-tolerated combination. This regimen produces results that appear equivalent to cisplatin–etoposide, but these have not been compared in a randomised study [8, 9].

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Carboplatin is a second-generation cisplatin analogue with reduced nephro-, oto-, neuro-, and gastrointestinal toxicity compared to cisplatin [10], with bone marrow toxicity as the dose-limiting factor.

Etoposide is frequently administered intravenously (i.v.) by daily infusion for 3–5 consecutive days, and has demonstrated schedule dependency in both preclinical and clinical trials [11]. Oral etoposide (150–300 mg/m^2) has variable absorption from the gastrointestinal tract, with a bioavailability of approximately 50% (range 25–75%). This variability necessitates a doubling of the oral dose compared to the i.v. dose. If the doses are appropriate, the efficacy and toxicity of oral and i.v. etoposide are similar [12].

Currently, randomised trials provide no evidence to suggest that an important advantage clinically has occurred in the cytotoxic therapy of SCLC with either an alternating strategy, maintenance chemotherapy or intensification strategy [1, 13]. In contrast, it has finally been established that thoracic irradiation (TI) adds to the benefit of chemotherapy. In patients with limited disease (LD), two separate meta-analyses pooling results from randomised trials, revealed a significant survival benefit in favour of TI [14, 15]. However, optimal radiation dose, schedule, timing of TI and treatment volume remain to be established. With adequate therapy, the median survival for

patients with LD should be more than 12 months and median survival in patients with extensive disease (ED) should be 8 months or more [1]. In the present study we aimed at confirming the results of Bishop and associates [16], who, in 1987, described the efficacy of carboplatin–etoposide in SCLC. However, contrary to that study and all other published studies of carboplatin–etoposide in SCLC, the primary goal of our study was to verify whether etoposide might be administered orally on an outpatient basis both in terms of efficacy, safety and feasibility.

MATERIALS AND METHODS

From March 1988 to June 1992, we registered and treated 106 consecutive, unselected and previously untreated patients with a cytological/histological diagnosis of SCLC and age below 70 years. We did not perform a regular phase II trial with informed consent. Instead, all patients referred to our department were treated according to a standard protocol with identical cytotoxic therapy. Staging and follow-up of all patients were performed according to a uniform strategy. No patients were excluded due to poor performance status or for any other reasons. Median age was 60 years (range 40–70) and median performance status (WHO) was 1 (range 0–4) (Table 1).

Pretreatment evaluation consisted of complete history, physical examination and full blood chemistry. Staging procedures in all patients included bronchoscopy and/or mediastinoscopy, X-ray or computerised tomography (CT) of the thorax, unilateral iliac crest biopsies and ultrasonography of the liver. CT of the brain was only performed in case of neurological symptoms.

LD was defined as tumour confined to one hemithorax including mediastinal and/or ipsilateral, hilar lymph nodes and/or ipsilateral, supraclavicular lymph nodes. ED denoted any involvement beyond these confines. Thus, 44 patients had LD and 62 had ED (Table 1).

Physical examination was repeated before each course of chemotherapy and X-ray of the thorax and ultrasonography of the liver (in patients with liver metastases) was performed after two and six courses of cytotoxic therapy and if progressive disease was suspected. Other imaging studies were performed when clinically indicated. After completion of therapy, clinical follow-up was performed every 3–6 months. Therapeutic efficacy was evaluated in terms of response, duration of response and survival. Response was defined according to WHO criteria [17], but not reviewed by an external board. Time to progression (TTP) was calculated as the time from start of cytotoxic therapy until definite progression or death. Survival was calculated from the first day of treatment to the date of death (for any reason) or last follow-up. All patients who received at least one dose were considered evaluable for response and toxicity. Adverse effects were graded according to WHO [17]. Complete blood cell counts were monitored 2 weeks after the first course of therapy, before each course of therapy, and upon request.

Table 1. Characteristics of 106 patients with small cell lung cancer treated with carboplatin and etoposide

	LD	ED	Total
No. of patients	44	62	106
Male	28	44	72
Female	16	18	34
Age (years)			
Median	61	60	60
Range	40–69	45–70	40–70
Performance status (WHO)			
0	12	4	16
1	23	30	53
2	7	15	22
3	2	9	11
4	0	4	4

LD, limited disease; ED, extensive disease.

Chemotherapy

Patients received carboplatin 300 mg/m^2 i.v. day 1 and etoposide 240 mg/m^2 orally days 1–3 (720 mg/m^2 per course) of a 4-week cycle. Carboplatin was administered as i.v. infusion over 60 min and etoposide as 50-mg capsules. Etoposide capsules were administered at bed time. If oral treatment was inconvenient, etoposide was given as an i.v. infusion (120 mg/m^2 for 3 days) over 30 min.

The dose of carboplatin–etoposide was adjusted according to platelet and white blood cell (WBC) counts ($\times 10^9$/l) on the scheduled day of treatment as follows: platelets $\geq$100 and WBC $\geq$3, 100%; platelets 75–99 or WBC 2.0–2.9, 50%. If platelets were <75 or WBC were <2.0, the treatment was postponed for 1 or 2 weeks. If patients experienced thrombocytopenia or leucopoenia WHO grade IV, the dose was reduced to 50–75%. Even though the bioavailability of capsule etoposide varies, a dose escalation or measurement of plasma levels was not part of our treatment strategy. All patients received prophylactic antiemetics (prednisolone and low-dose metoclopramide or metopimazine) before infusion was commenced, and on request. Therapy was repeated for six cycles or until progression.

Radiotherapy

The value of TI in patients with LD was uncertain at the time this study was initiated but, in 1992, two independent meta-analyses [14, 15] showed a survival benefit in favour of TI. However, during our study, TI was given on the discretion of the treating physician. TI was offered to patients with LD, who achieved complete response (CR) or partial response (PR) within two courses of carboplatin–etoposide. The volume treated included the primary tumour (defined by prechemotherapy chest X-ray) with a 2-cm margin, the mediastinal lymph nodes and ipsilateral pulmonary hilus. Opposing antero-posterior fields were used with daily treatment 5 days a week. Treatment was given on a linear accelerator with at least 4 MV X-rays. The spinal cord or oesophagus was not shielded. The irradiated volume was defined by individually shaped portals, the heart and the contralateral lung were shielded as much as possible using 5-cm lead blocks. TI was started 1 week after course three, and given as split course therapy, delivering 22, 50 Gy in 11 equal fractions both after course three and four (total dose: 45 Gy in 22 fractions). 29 patients received TI, median-field size was 130 cm^2 (range 80–180). In 16 patients, the width of the treatment field was reduced 1 or 2 cm during the second part of TI. Prophylactic cranial irradiation was not given.

Statistics

Survival and TTP were calculated by the Kaplan–Meier plot [18]. All median values are followed by range, and frequencies expressed in percentages are followed by 95% confidence intervals (CI).

Table 2. Analysis of response, time to progression and survival in 106 patients treated with carboplatin and etoposide

	n	OR (%)	CR (%)	TTP (months)	MS (months)
LD	44	89	41	11	15
95% CI (range)		(75–97)	(26–57)	(1–42)	(1–45)
ED	62	53	8	6	8.5
95% CI (range)		(40–66)	(2–18)	(0–24)	(0–26)
Total	106	67	21	7	10.5
95% CI (range)		(58–77)	(14–31)		

Median observation time: 30 months. Limited disease (LD), 11 patients alive. Extensive disease (ED), 3 patients alive. 95% CI, 95% confidence interval; OR, overall response; CR, complete response; TTP, median time to progression; MS, median survival.

RESULTS

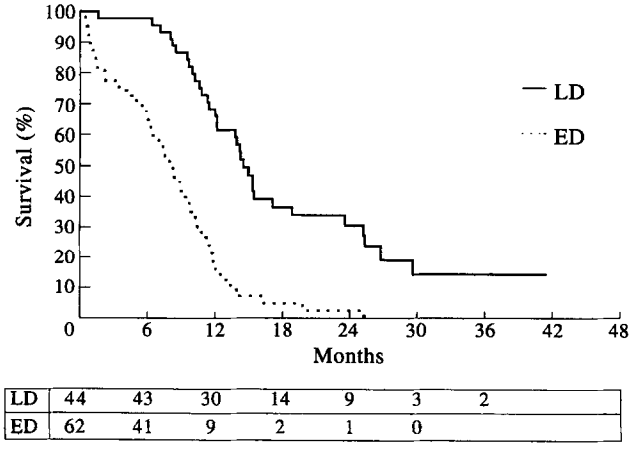
106 patients (72 men and 34 women) received at least one course of carboplatin–etoposide. At a median observation time of 30 months, all 106 were considered evaluable for response and toxicity according to the criteria previously mentioned. Objective response (CR and PR) was seen in 89% (CI 75–97%) of patients with LD and in 53% (CI 40–66%) with ED (Table 2). Complete response was seen in 41% (CI 26–57%) of patients with LD and in 8% (CI 2–18%) with ED (Table 2). Overall response rate was 67% (CI 58–77%) with complete response in 21% (CI 14–31%).

All 106 patients were evaluable for survival (Figure 1) and TTP. Patients with LD had a median TTP of 11 months (range 1–42) and a median survival of 15 months (range 1–45). Survival was estimated to be 34% (CI 19–49%) at 24 months and 14% (CI 2–28%) at 36 months. Patients with EO had a median TTP of 6 months (range 0–24) and a median survival of 8.5 months (range 0–26); 3 patients are alive. Survival was estimated at 16% (range 6–26%) at 12 months. Overall median survival was 10.5 months (range 0–45) (Table 2).

Ninety-three per cent (CI 81–99%) of patients with LD and 60% (CI 46–72%) of patients with ED completed the planned six courses of carboplatin–etoposide. Oral treatment was convenient for most patients and therapy well tolerated (Table 3).

However, in 9 patients (20%; CI 9–36%) with LD and 26 patients (42%; CI 29–56%) with ED at least part of etoposide was administered i.v. for various reasons. 11 patients with ED and a very poor performance status started and continued treatment with i.v. etoposide at the discretion of the treating physician. Median number of courses in these patients was as low as one (range 1–3). In 5 patients, etoposide was partly administered i.v. due to poor performance. 15 patients stated they were not able to swallow the big capsules, 2 patients felt that oral etoposide exacerbated nausea and 1 patient developed oesophagitis after radiotherapy.

101 patients (95%; CI 89–99%) received 100% of the planned



LD	44	43	30	14	9	3	2
ED	62	41	9	2	1	0	

Figure 1. Survival of 106 small cell lung cancer patients treated with carboplatin/etoposide. The numbers of patients at risk are indicated below.

Table 3. Tolerability of carboplatin and etoposide (oral and/or intravenous (i.v.)) in 106 patients with small cell lung cancer

Number of courses and mode of administration of carboplatin–etoposide	N_{LD}*	N_{ED}°
Oral therapy		
Oral ×6	33	26
Oral <6	2	10
Oral and i.v. therapy		
Oral + i.v. ×6	8	10
Oral + i.v. <6	0	5
i.v. therapy		
i.v. ×6	0	1
i.v. <6	1	10
Reduced dose	0	5
Reason for i.v. therapy		
Oesophagitis during TI	1	
Dysphagia	8	7
Poor performance status		16
Nausea		3

* Total, $n=44$. ° Total, $n=62$.

dose for six courses or until progressive disease was determined. 4 patients had a dose reduction of carboplatin and etoposide due to haematological toxicity. The total dose in these 4 patients was 75% (range 50–90%). One patient received etoposide at a dose of 50% due to hepatic dysfunction and he only received one treatment course. Haematological toxicity WHO grade IV was seen in 16 patients (15%; CI 8–24%). WHO grade IV leucopenia was observed in 13 patients (12%; CI 6–21%) and WHO grade IV thrombocytopenia in 11 patients (10%; CI 5–18%) (Table 4)). 5 patients with LD experienced haematological toxicity grade IV and, in all cases, when the second part of TI was given. Due to this, dose reduction was not effected during the last two courses of cytotoxic therapy, which were administered without grade IV toxicity in all cases. 11 patients with ED had haematological toxicity grade IV, in 6 patients dose reduction was not necessary as grade IV was seen after the final course of therapy (median number of courses was one; range 1–5). One patient with liver metastasis and marked elevation of serum lactate dehydrogenase and alkaline phosphatase but normal bilirubin, had grade IV leucopenia after the first course of carboplatin–etoposide. Dose was erroneously not reduced during the subsequent courses, but hepatic biochemical tests normalised and no severe haematological toxicity was seen.

Using the present cytotoxic schedule, we did not observe a cumulative myelotoxicity. One patient died of sepsis during leucopenia. This patient with ED and poor performance died 2 weeks after the first course of therapy. Nausea/vomiting was usually mild. Alopecia occurred in all patients. No neuro- or ototoxicity were observed. We found no increase in serum creatinine during treatment with carboplatin.

Site of relapse was evaluated in patients with LD. 14 patients had no sign of recurrent disease at the last clinical follow-up examination. Among 30 patients with known relapse, 13 patients had local recurrent disease, 12 patients developed brain metastases, 1 patient meningeal carcinomatosis, 1 patient medullary compression, 2 patients liver metastases, and 1 patient had bone metastasis.

DISCUSSION

The current medical strategy for treating SCLC is the design of more active and/or less toxic regimens. However, in the past decade, no major improvement in cytotoxic therapy has been seen [1]. With optimal therapy, median survival exceeds 12 months in patients with LD and 8 months in patients with ED [1].

The inclusion of cisplatin–etoposide or the addition of etoposide into other regimens yields a highly active treatment and such combinations are often considered the standard therapy for SCLC [2, 19]. Despite the lack of randomised trials substituting carboplatin for cisplatin, comparable studies show similar response rate and survival gains for both drugs [8]. Significantly, carboplatin therapy yields much lower toxicity than cisplatin.

Table 4. Toxicity of carboplatin and etoposide in small cell lung cancer

	WHO grade				
	0	1	2	3	4
Leucopenia (%)	48	17	15	8	12
Thrombocytopenia (%)	72	9	3	6	10
Nausea/vomiting (%)	15	34	24	27	

All patients had alopecia requiring a wig.

Bishop and colleagues [16] and Smith and colleagues [20] were the first to publish the use of carboplatin–etoposide in SCLC. Smith and associates [20] reported on 52 patients with SCLC given carboplatin 300 mg/m^2 i.v. and etoposide 100 mg/m^2 i.v. days 1–3. The response rate was 82% in patients with LD and 88% in ED. However, duration of response was short, and median survival in LD as short as 9.5 months.

Bishop and associates [16] performed a phase II trial of carboplatin–etoposide in 90 previously untreated patients. Carboplatin was given as 100 mg/m^2 i.v. days 1–3 (300 mg/m^2 per course) and etoposide as 120 mg/m^2 i.v. days 1–3 (360 mg/m^2 per course). This treatment was well tolerated, with an overall response rate of 77%, and a median survival in LD of 15 months compared to 8 months in ED. Encouraged by the results of Bishop and associates [16], we started to use the combination carboplatin–etoposide in 1988. However, contrary to that study [16], we intended to treat patients on an outpatient basis. We, therefore, chose a standard strategy of oral etoposide (if feasible) and, furthermore, patients received the total dose of carboplatin i.v. in 1 h.

Since those two publications, the use of carboplatin and etoposide has been reported in nine additional studies [21–29], either as a two-drug regimen or in combination with other cytotoxic drugs. Tables 5 (limited disease) and 6 (extensive disease) summarise the 11 published studies evaluating carboplatin/etoposide containing regimens in SCLC.

In summary, the response rates—and even more importantly TTP and survival in the present study of oral etoposide—are very similar to results obtained from trials where cytotoxic therapy was given i.v. (Tables 5 and 6). Response rates in patients with ED are overshadowed by the excellent results in patients with LD. This discrepancy might be explained by the fact that we included 13 patients with a performance status of 3 or 4. Although such patients are often excluded from phase II or III trials, no patients were excluded from the present study because we believe in the importance of presenting a wholly unselected, consecutive group of patients. Moreover, it is noted that the dose intensity is rather low, since only 4 patients required a dose reduction due to haematological toxicity. If the dose of etoposide had been escalated in patients with grade 0 or 1 haematological toxicity, or if the dose of etoposide was adjusted according to plasma levels, the response rate might have been greater. Nevertheless, TTP and survival were comparable to results obtained in other studies (Table 6).

Oral administration of etoposide has not been reported in other published studies, but this allows patients to be treated in an outpatient setting with one single visit. This is important for health care costs in many countries. In addition, it may be more convenient for most patients and thereby contribute to quality of life. If survival gain is preserved, an improvement in overall results is obtained.

Quality of life assessment was not part of the standard strategy in our department, but in an on-going prospective study of carboplatin and etoposide, we are evaluating quality of life.

In a total of 106 unselected, consecutive patients with SCLC treated according to the same regimen, we obtained a median survival of 10.5 months (LD 15 months; ED 8.5 months). Even though the study is retrospective, this outpatient regimen of carboplatin and oral etoposide has a therapeutic efficacy similar to other regimens used in patients with SCLC.

Randomised trials are required to determine whether these results are as good as those achieved with other combinations. Until such trials prove otherwise, it is reasonable to use etoposide

Table 5. Summary of published studies of carboplatin and etoposide containing regimens as first-line therapy in SCLC, limited disease

Reference	CT	*n*	OR (%)	CR (%)	MS (months)
Bishop 1987 [16]	CaE	35	77	40	15
Smith 1987 [20]	CaE	28	82	29	9,5
Humblet 1989 [25]	CaEEpi	43	98	28	16
Thatcher 1989 [26]	CaEIO	42	79	57	14
Bishop 1990 [24]	CaECO	40	83	60	13
Smith 1990 [22]	CaEI	18	94	72	16
Gatzemeier 1992 [23]	CaEO	63	90	56	13
Total		269	86	48	9–16
(95% confidence limits)			(81–90)	(41–55)	
Present study	CaE	44	89	41	15

OR, overall response; CR, complete response; MS, median survival; CT, chemotherapy; Ca, carboplatin; E, etoposide; C, cyclophosphamide; I, ifosfamide; O, vincristine; Epi, epirubicin.

Table 6. Summary of published studies of carboplatin and etoposide containing regimens as first-line therapy in SCLC, extensive disease

Reference	CT	*n*	OR (%)	CR (%)	MS (months)
Bishop 1987 [16]	CaE	55	58	9	8
Smith 1987 [20]	CaE	24	88	13	9,5
Evans 1988 [27]	CaE	32	56	16	8
Wolf 1991 [21]	CaE	25	40	12	9.3
Luikart 1993 [29]	CaE	48	63	17	12
Humblet 1989 [25]	CaEEpi	40	78	10	>9
Bishop 1990 [24]	CaECO	50	76	22	9.5
Smith 1990 [22]	CaEI	14	100	29	9.5
Gatzemeier 1992 [23]	CaEO	58	83	35	9.5
Gatzemeier 1992 [28]	CaEO	93	81	32	9.5
Total		481	73	24	8–12
(95% confidence limits)			68–77	20–28	
Present study	CaE	62	53	8	8.5

Abbreviations: see Table 5.

administered as capsules in conjunction with substituting carboplatin for cisplatin.

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Pharmacokinetics, Metabolism and Clinical Effect of Ifosfamide in Breast Cancer Patients

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Ifosfamide (IFO) at a dose of 5 g/m², was administered as a 24-h infusion to 15 patients with metastatic (12) or locally advanced (3) breast cancer (age range 33–59 years, median 46). Concurrent chemotherapy was doxorubicin (40 mg/m²) or epirubicin (60 mg/m²). Ifosfamide and its metabolites were measured in plasma and urine during and for 24 h after the infusion using a high performance thin layer chromatography (HPTLC) technique. Patients' haematological toxicity and biochemistry were monitored during treatment and patients were followed for up to 2 years after therapy. At the time of evaluation, 5 of the patients were alive, 2 of whom had not relapsed. A marked variation was observed in the pharmacokinetics and metabolism of ifosfamide in the evaluable patients. Clearance, volume of distribution and half-life of the drug were 3.48 ± 0.88 l/h/m², 0.56 ± 0.22 l/kg and 4.68 ± 2.01 h, respectively. There was no apparent correlation between these pharmacokinetic variables and patient age, weight or renal function. AUCs of the ultimate alkylating species isophosphoramide mustard (IPM) varied over 6-fold, as did those of the inactivated metabolite carboxyifosfamide (CX). AUCs of dechloroethylated metabolites varied 4-fold (3-dechloroethylifosfamide, 3-DCI) or 8-fold (2-DCI), while that of the parent compound varied only 2.5-fold. Variation in recovery of the metabolites in urine varied over an even wider range, total recovery varying from 17.5 to 81.8% of the dose administered. There was little apparent correlation between pharmacokinetic and metabolite parameters of IFO and haematological toxicity. However, there was a marked negative correlation between both progression-free interval and survival and the AUCs of the products of IFO activation (IPM and CX). In addition, the recovery of IPM in urine was higher in patients experiencing a partial response compared to those with progressive or stable disease. Recovery of dechloroethylated metabolites correlated positively with survival, if 1 poor prognosis patient was excluded. Although far from conclusive, these results give some insight into a possible mechanism of action of ifosfamide and indicate that some species other than IPM, as measured systemically, is responsible for the pharmacological effects of this drug.

Key words: ifosfamide, pharmacokinetics, metabolism, variability, clinical response
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