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Carboplatin as Second Line Treatment for Recurrent or Progressive Brain Metastases From Small Cell Lung Cancer

H.J.M. Groen, E.F. Smit, H. Haaxma-Reiche and P.E. Postmus

Patients with brain metastases from small cell lung cancer (SCLC) have a poor prognosis. Although most patients die from metastatic disease outside the central nervous system, this disabling metastatic site often needs treatment to mitigate the signs and symptoms of intracranial disease. The effect of carboplatin (400 mg/m² every 4 weeks) as second line treatment for recurrent or progressive brain metastases was studied in 20 SCLC patients. 19 patients could be evaluated: 16 by contrast enhanced brain computer tomography (CT) scan (2 patients had complete response, 6 partial response, 4 stable disease and 4 progressive disease) and 3 patients clinically, who had progressive disease. The objective response rate in the brain was 40% (95% CI:22–61%). The median response duration was 8 weeks (range 2–29). The median survival was 15 weeks (range 1–44). Previous cranial irradiation appeared to be beneficial for survival. There was only mild haematological and gastrointestinal toxicity. Carboplatin has activity against brain metastases and gives palliation in responding patients.
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INTRODUCTION

COMBINATION CHEMOTHERAPY in small cell lung cancer (SCLC) improves median and long-term survival [1]. The management of brain metastases in SCLC is an important clinical problem. In more than 40% of SCLC patients symptomatic brain metastases will develop [2]. In addition, with prolonged survival, the incidence of brain metastases increases [3].

Measures to reduce the high relapse rate in the brain have been unsuccessful. Although prophylactic cranial irradiation (PCI) reduces the clinical relapse rate from 23 to 6% [2, 4], the value of PCI is controversial, due to limited effect on survival and long-term neurological sequelae [4, 5]. Treatment of brain metastases with whole brain radiotherapy (WBRT) has been standard for decades. For patients with intracranial relapse after radiotherapy (PCI or WBRT), retreatment with radiotherapy is usually unfeasible. For these patients chemotherapy may be a modality of further palliation. In two previous studies from our group it has been shown that brain metastases responded to treatment with podophyllotoxin derivatives in about 40% of the patients [6, 7]. The durations of these radiologically proven responses were comparable to the durations of clinical responses after WBRT [8–10].

In this report we describe the results of carboplatin, one of the most active agents against SCLC, for SCLC patients with progressive brain metastases, after treatment failure with teniposide, etoposide or cranial irradiation.

PATIENTS AND METHODS

Patients

From January 1987 until March 1992, 20 patients have been entered into this prospective study. Criteria for eligibility were: histologically or cytologically proven SCLC, leucocyte count $> 3.0 \times 10^9$/l, platelet count $> 100 \times 10^9$/l, serum creatinine < 150 μmol/l, progressing brain metastases proven with contrast enhanced brain computed tomography (CT) during or shortly after treatment with teniposide, reinduction combination chemotherapy or cranial irradiation for symptomatic brain metastases. Patients, who previously received carboplatin, were not eligible. Informed consent was obtained from all patients. 2

Correspondence to H.J.M. Groen.
H.J.M. Groen, E.F. Smit and P.E. Postmus are at the Department of Pulmonary Diseases; and H. Haaxma-Reiche is at the Department of Neurology, University Hospital Groningen, Oostersingel 59, 9713 EZ Groningen, The Netherlands.
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elderly patients with a good performance insisted on treatment and were included.

Therapy

The administration of carboplatin at a dose of 400 mg/m^2 was planned every 4 weeks. Carboplatin was diluted in 250 ml dextrose 5% and administered as an intravenous (i.v.) infusion over 30 min in the outpatient department. Treatment was continued either until intracranial progression, established clinically or by CT, or extracranial progression developed. Dose reductions were not allowed for. If bone marrow recovery was not complete at the time the next course was due, treatment was delayed until recovery had been sufficient. Dexamethasone (4 mg, 6-hourly) was given if oedema due to brain metastases was found on CT and considered to contribute significantly to the neurological symptoms. As soon as these symptoms subsided, dexamethasone was tapered off and whenever possible stopped.

Response criteria

Response in the brain was evaluated after each course by clinical investigation and after two, four and six courses by CT scans. Clinical investigations included physical examination, evaluation of neurological signs and symptoms, performance score according to ECOG, complete blood cell count, blood chemistry and chest X-ray.

Complete response (CR) in the brain was defined as complete disappearance of tumour lesions on CT with disappearance or stabilisation of neurological signs and symptoms. Partial response (PR) was defined as a decrease of 50% or more of the product of the perpendicular diameters of an enhancing lesion on the CT and/or a similar reduction in the sum of the products of the perpendicular diameters of enhancing lesions on CT and/or a reduction in number without otherwise signs of progression. Stable disease (SD) was defined as an increase of less than 25% or a decrease less than 50% of the enhancing lesions without developing new lesions and no worsening of neurological symptoms. Progressive disease (PD) was defined as an increase of more than 25% or appearance of new metastases or neurological worsening attributed to metastases.

Extracranial disease was evaluated after each course with clinical investigations and chest X-rays. Responses were evaluated according to standard criteria. [11].

Survival and response duration were measured from the first day of the treatment with carboplatin. Overall survival was measured from the start of the primary treatment until death. Survival differences were analysed with SSPS PC + using the Lee–Desu statistic.

Early death is death due to tumour progression before the first evaluation after the start of therapy. Toxicity was scored during each course according to the WHO-criteria, evaluated between day 14 and day 21 in the outpatient department.

RESULTS

Patients

In this study, 20 patients, 18 male and 2 female, with a median age of 53 years (range 40–81) were entered. 4 patients presented with brain metastases and received teniposide ($n = 2$) or teniposide with WBRT ($n = 2$) as initial treatment. 12 patients received systemic treatment without PCI. After relapse in the brain, 5 patients received teniposide 150 mg/m^2 and 6 received teniposide with WBRT. 1 patient received first reinduction cyclophosphamide, doxorubicin and etoposide (CDE) for intrathoracic recurrence and later WBRT for brain metastases. When progression in the brain recurred, carboplatin was started.

4 patients received systemic treatment with PCI. After relapse in the brain 2 patients were treated with teniposide and 2 patients received reinduction CDE for intra- and extracranial relapse. On recurrence in the brain the study treatment was started. All patients, except 1 responded to first line treatment, including 6 complete responders. One patient had PD in the brain after teniposide (Table 1).

PCI (4 patients) and WBRT (9 patients) both at a dose of 30 g, had been given more than 2 months before entry into this study. The period between the last treatment for brain metastases and the start of carboplatin was less than 3 months in 13 patients and in 7 patients it was more than 3 months. At the start of carboplatin treatment the performance score was 1 in 11 patients, 2 in 5 patients and 3 in 4 patients.

Response

5 patients each received one course of carboplatin, two courses, three courses, and more than three courses.

19 patients were evaluable for response, 1 patient aged 54 with performance score 3 died 6 days after the start of carboplatin treatment and was considered as PD. 16 patients were evaluated with contrast enhanced brain CT. CT evaluation was not performed in 3 patients, who had obvious clinical progression. These patients were considered as treatment failures.

Of the patients who were evaluable by CT, 2 patients had CR, 6 patients had PR and 4 had SD. 4 patients had PD. The total response rate was 8/20 (40%, 95% CI:22–61%). The median response duration was 8 weeks (range 2–29). Of the 8 responders on brain CT, 2 patients became asymptomatic, 4 patients showed neurological improvement and 2 patients had neurological stabilisation of their signs and symptoms. The complete responders had minor residual neurological deficits. The response rate in patients with and without previous cranial irradiation was 5/13 and 3/7, respectively.

Concerning the extracranial response, 18 patients were evaluable. 5 patients had PR, 9 SD and 4 PD. The extracranial

Table 1. Patients' characteristics on entry to the study

Male/Female		18/2
Median age (range)		53 (40–81)
Initial treatment for SCLC:	CDE	13
	ACO	2
	Etoposide	1
	Teniposide (T):	4*
Best response to first treatment:	CR	6
	PR	13
	SD	0
	PD	1
Previous interventions for brain metastases:	WBRT+T	8
	PCI+T	2
	T	7
	PCI	2
	WBRT	1
Performance score:	0	0
	1	11
	2	5
	3	4
Number of brain metastases:	1	7
	2	4
	≥ 3	9

* Presented with brain metastases.

Table 2. The relation between treatment-free interval before start of carboplatin, response of intracranial metastases and median survival time in 20 pretreated SCLC patients

	Therapy-free interval < 3 months	> 3 months
n	13	7
Response		
CR	2	0
PR	3	3
SD	2	2
PD	2	2
Clinical PD	4	0
MST weeks (range)	14 (1–31)	21 (7–44)*

MST = median survival time; * $P = 0.25$.

response was 5/20 (25% with 95% CI:11–47%). 11 patients received corticosteroids for oedema surrounding metastases. 5 of these patients could stop within 4 weeks and in 2 patients it was possible to decrease their dexamethasone dose from 16 to 4 mg daily. 9 patients did not use steroids.

Median survival for the whole group was 15 weeks (range 1–44). The median survival in the group with a treatment-free period of less than 3 months before the start of treatment with carboplatin was 14 weeks (range 1–31), as opposed to 21 weeks (range 7–44) for patients with a treatment-free period of more than 3 months. The difference between these groups was not significant ($P = 0.25$). 5 out of 13 patients with a treatment-free period < 3 months responded, compared with 3/7 with a treatment-free period > 3 months (Table 2).

The median survival in the group without previous cranial irradiation ($n = 7$) differed significantly from the median survival in the group with previous cranial irradiation ($n = 13$): 8 weeks (range 1–16) versus 21 weeks (range 7–44) ($P = 0.01$). The survival plots are shown in Fig. 1. The overall median survival, measured from the start of the first antitumour treatment, for the group without and with cranial irradiation also differed: 48 weeks (range 16–92) and 80 weeks (range 44–204),

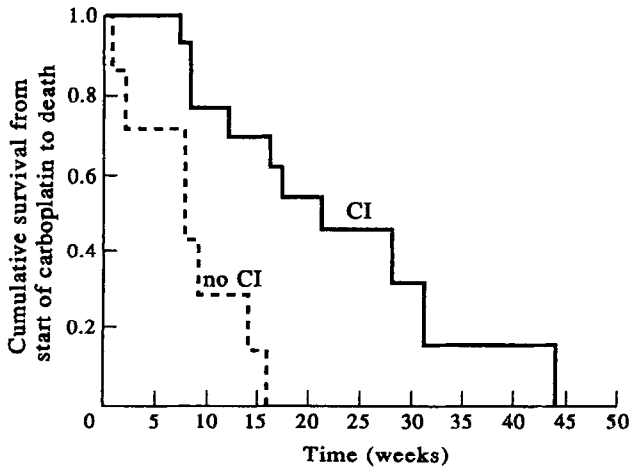

Fig. 1. Survival plots from the start of carboplatin treatment for patients without and with previous cranial irradiation (CI).

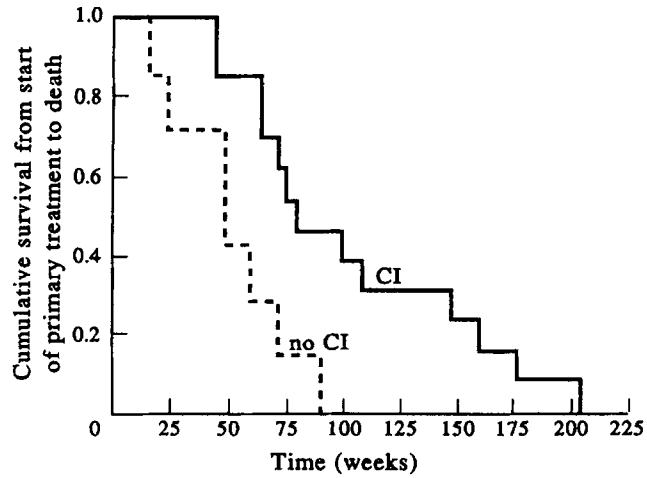

Fig. 2. Survival plots from the start of the first antitumour treatment for patients with and without previous cranial irradiation (CI).

respectively ($P = 0.02$) (Fig.2). Nevertheless the median duration from the primary treatment until the arise of brain metastases is equal in both groups: 40 vs. 44 weeks (excluding 4 patients, who presented with brain metastases) (Table 3).

If we exclude 4 PCI patients from the cranial irradiation group and compare the survival between the 9 patients with WBRT and the 7 patients treated with teniposide only, then the survival difference still exists ($P = 0.019$).

Toxicity

Fifty-five courses of carboplatin have been administered. In 7% of the courses WHO grade 3 leukocytopenia and no grade 4 was observed. WHO grade 3 anaemia was seen in 4% of the courses. Forty-one per cent of the patients had WHO grade 3 and 4% WHO grade 4 thrombocytopenia. During one course, platelet transfusions were given. No aplasia-related septicaemia was noted. Nausea and vomiting were mild and easily controlled by antiemetics.

Table 3. Response of brain metastases, median duration from primary treatment until brain metastases and median survival time in 20 pretreated SCLC patients with and without cranial irradiation (CI)

	With CI	Without CI	
n	13	7	
Responses			
CR	1	1	
PR	4	2	
SD	3	1	
PD	3	1	
NE	2	2	
Overall MST weeks (range)	80 (44–204)	48 (16–92)	$P = 0.02$
MST weeks (range)	21 (7–44)	8 (1–16)	$P = 0.01$
MDT weeks (range)	44 (12–160)	40 (28–48)*	$P = 0.86$

Overall MST = median survival time, measured from start of primary treatment until death. MST = median survival time, measured from the start of carboplatin treatment until death. MDT = median duration from primary treatment until the arise of brain metastases. NE = not evaluable. * Excluding 4 patients, who presented with brain metastases.

DISCUSSION

Treatment of brain metastases of SCLC with chemotherapy has long been ignored, because of presumed inaccessibility of the brain parenchyma for chemotherapy. However, the blood–brain barrier (BBB) may behave differently in pathological situations than under physiological circumstances. First line chemotherapy for brain metastases seems to induce almost comparable responses on intra- as well as extracranial disease in studies with small numbers of patients [12–15]. Adding drugs, which are supposed to cross the BBB, to first line therapy for SCLC did not result in a reduction of brain metastases [16].

Second line treatment for SCLC is known to be rather ineffective. Carboplatin as a single agent is probably the most active agent in pretreated patients [17–20]. Smit *et al.* reported an extracranial response rate of 37% with a treatment of carboplatin in combination with vincristine [21]. In combination with ifosfamide the response rate was over 50% in so-called resistant patients, with a relapse within 3 months after chemotherapy [22]. In our study a 40% response rate was seen in intracranial and 25% in extracranial lesions. Once again this study shows that the response rate of brain metastases of SCLC is comparable to the response of the tumour outside the central nervous system. The response rate was not different if we compare those with a treatment-free period of more and less than 3 months. Median survival tended to be longer, but this was not statistically significant. The results of our study also suggest that previous cranial irradiation is beneficial in chemotherapeutically treated patients with brain metastases. Although a bias in patient selection cannot be excluded, the survival benefit of the irradiated group is remarkable. The time elapsed since primary treatment and development of brain metastases cannot account for this survival advantage as this was equal in both groups. A possible bias of initial CR patients selection for PCI was also excluded.

The main goal of cytostatic therapy in these patients was palliation. The clinical improvement of responders and the limited duration of high-dose steroid treatment are important aspects of this palliation, while toxicity was mild. The predominant form of toxicity was thrombocytopenia, which was not problematic as platelet transfusions were administered to 1 patient only. Nausea and vomiting were easily controlled with antiemetics.

In conclusion, the data of our study suggest that clinical benefit is achieved on an outpatient basis in responding patients by single agent carboplatin. This approach should be considered as palliative treatment for recurrent or progressive brain metastases, especially in patients with simultaneous tumour progression in and outside the brain and in previously irradiated patients.

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