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Brain Metastases from Small Cell Lung Cancer Treated with Combination Chemotherapy

PAUL E.G. KRISTJANSEN and HEINE H. HANSEN
Department of Oncology ONB, Finsen Institute, Copenhagen

Abstract—*Ten patients with metastatic small cell lung cancer (SCLC) in the brain, shown by CT scan at time of diagnosis, were treated with systemic combination chemotherapy. Repeated CT scans were performed every 4 weeks. Seven patients were evaluable, since three patients died during the first 2–3 weeks. Significant responses on CT scans as well as neurologic improvement were demonstrated in all evaluable patients. Four of seven patients obtained a complete response in the brain, while three had partial remissions. The impact of this observation on the overall treatment strategies in SCLC has further to be defined.*

INTRODUCTION

BRAIN METASTASES are a frequent complication of small cell lung cancer (SCLC). The incidence as well as the risk of development increases with prolonged survival, as predicted in 1973 by Hansen [1] and confirmed in more recent studies [2]. The CNS has hitherto been regarded as a sanctuary for metastatic tumor cells, thus limiting the prospects of long term survival and cure. The risk of developing brain metastases at 2 year survival is as high as 50%, while the incidence at diagnosis is 10% [2–4]. Due to a presumed lack of adequate drug penetration into brain tumors, radiation therapy is usually the treatment of choice in patients with brain metastases. The prognosis for patients with SCLC who present with initial or relapsed brain metastases is significantly different. The latter indicates an extremely poor prognosis, while patients with initial brain metastases as the only sign of extensive disease seem to have a survival similar to that of patients with limited disease [3]. This is also reflected in multivariate analysis indicating that initial brain metastases are not associated with a particularly poor prognosis when other factors are excluded [4].

An impact of brain metastases on the integrity of the blood–brain barrier is demonstrable to some extent by iodine-contrast uptake in CT scans [5].

It seems likely therefore that both the intracranial susceptibility and the intratumoral sensitivity to chemotherapy are more pronounced in initial CNS metastases than at relapse.

Notable responses to chemotherapy as the sole treatment of primary and metastatic germ cell tumors in the brain and of initial brain metastases from breast cancer have recently been published [6–8]. Corresponding results in metastatic SCLC have been described only as single cases [9, 10]. The present report describes how intracranial brain tumors, demonstrated by CT scan, in patients with small cell lung cancer respond to chemotherapy.

PATIENTS AND METHODS

Since 1985, 10 SCLC patients with brain metastases at time of admission were treated at the Finsen Institute with chemotherapy alone (Table 1). At first this new therapeutic approach was not part of any planned program. Only the last four patients of the present series were entered in an ongoing prospective evaluation of the issue, initiated after the first encouraging results were achieved. Diagnostic specimens to establish the primary diagnosis of SCLC were evaluated by pulmonary pathologists at our institution, using the World Health Organization (WHO) criteria [11]. All patients had SCLC, and in addition one patient (No. 10) exhibited combined subtype (small cell/large cell) while another (No. 4) had focal elements of adenocarcinoma.

All patients underwent pretreatment staging procedures including bilateral bone marrow examination and peritoneoscopy or ultrasound examination with biopsy of the liver.

Presenting signs and symptoms

The dominant neurological symptoms and fin-

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Correspondence and reprint requests to: Heine H. Hansen, Dept. ONB, Finsen Institute, 49 Strandboulevarden DK-2100, Copenhagen, Denmark.

Table 1. *Patient characteristics*

Patient No. sex age	Performance status ECOG	Clinical neurologic presentation	Brain CT scan lesions	Additional disease sites	Biopsy site and histology
1 male 68	—	Gait disorder, hemilateral muscle weakness, mild aphasia	3 cerebral	Lung	Transcutaneous lung biopsy, SCCL
2 male 51	1	Headache, vertigo	4 cerebral 1 cerebellar	Lung	Bronchoscopy, SCCL
3 male 59	2	Double vision, headache Extracranial skull tumor	>5 lesions	Lung Liver	Bronchoscopy, skull tumor, SCCL
4 male 51	1	Headache, nausea, blurred vision	Multiple bilateral cerebral and cerebellar	Supraclavic node	Bronchoscopy, lymph node, SCCL + adenocarcinoma
5 male 68	1	Vertigo, hemilateral muscle weakness	>5 lesions	Mediastinum	Mediastinoscopy SCCL
6 female 57	2	Vertigo, hemiparesis	Multiple lesions bilaterally	Lung	Bronchoscopy, mediastinoscopy, SCCL
7 female 60	2	Hemiparesis	Cystic lesion in frontal lobe	Lung	Bronchoscopy, SCCL
8 male 67	1	Gait disturbances, vertigo, headache, double vision	Cerebellar lesion	Lung	Transcutaneous lung biopsy, SCCL
9 female 60	2	Vertigo, nausea	Cerebellar lesion	Lung	Fine needle aspiration from lung tumor, SCCL
10 male 54	4	Ataxia, dysartria	Multiple cerebellar and cerebral lesions	Lung	Bronchoscopy, small cell/large cell

dings, as described in the records of the referring general hospitals or found at pretreatment examination at admission to our department, are shown in Table 1. Lumbar puncture was performed in six patients, all with normal spinal fluid examination, including cytology, protein, glucose and lactate dehydrogenase concentration. All patients had normal bone marrow examination and only one patient had liver metastasis.

Evaluation

The initial diagnosis of the CNS tumors were based on neurologic examination and brain CT scan with intravenous contrast. This report deals primarily with the roentgenologic response as shown by a review of successive CT scans performed every 4 weeks on the same equipment.

The brain responses based on CT scans were characterized as follows:

(a) Complete remission (CR): complete disappearance of all disease parameters.
(b) Partial remission (PR): more than 50% reduction in the square product of two perpendicular diameters;
(c) No change (NC) has an upper threshold at 25%;
(d) Progressive disease (PD): more than 25% increase of a parameter or appearance of new brain metastases.

Responses outside the CNS were evaluated according to the WHO criteria [12].

Table 2. Treatment results

Patient No.	Treatment*	Survival†	Response		Duration of CNS remission	Site of relapse
			Peripheral	CNS		
1	I	74 w+	CR	CR	68 w+	Thorax
2	II	32 w	PR	CR	17 w	Brain, lung, skin
3	II	30 w	PR	PR	16 w	Brain, lung, skin
4	III	26 w+	CR	CR	20 w	Brain
5	III	12 w	CR	PR§		—
6	III	10 w	CR	CR§		—
7	III	18 w+	NC	PR‖		Lung
8	III	16 days	(died 2nd to malignant diease)			
9	III	14 days	(died 2nd to malignant disease)			
10	III	15 days	(died 2nd to GI bleeding)			

*I: CCNU 70 mg/m^2 p.o.; CTX 1000 mg/m^2 i.v. q 4 week; VCR 2.0 mg i.v. II: as I plus VP-16 70 mg/m^2 p.o. days 3–6 q 4 week [22]. III: VM-26 50 mg/m^2 i.v. days 1–5; *cis*-DDP 35 mg/m^2 i.v. days 2–3 q 4 week; VCR 1.3 mg/m^2 i.v. day 1 (plus 8 and 15 in first cycle).

†From start of treatment.

‡Cerebral hemorrhage at 15 weeks.

§Autopsy included brain examination.

‖Reduction from 5 × 2.5 × 2.5 cm to 3.5 × 2 × 2 cm.

Treatment

Treatment schedules are shown in Table 2. Patient No. 1 continued on the three-drug combination (I) for 11 months in CR until pulmonary relapse. The patient is at present receiving mono-drug therapy with etoposide 90 mg/m^2 i.v. × 5 days 1–5, q 4 weeks, still with neither clinical nor radiological signs of CNS metastases. Patient No. 2 had four cycles of the four-drug combination (II). The patient obtained a PR and remained on continuous oral treatment with cyclophosphamide and etoposide until PD.

Acute neurosurgery was performed on patient No. 9, who developed acute hydrocephalus on day 3. A ventriculo-peritoneal shunt was inserted. Patient No. 10 died on day 15 during an operation for an acute bleeding gastric ulcer.

All patients had initial high-dose glucocorticoid treatment for at least 1 week (prednisolone 150 mg/day orally or dexamethasone 24 mg/day i.v.) followed by individually graded dose reduction.

RESULTS

Neurologic clinical improvement was reported in all evaluable patients (Nos. 1–7), ranging from complete alleviation in three patients to moderate but evident improvement in two. The relative contribution of steroids and chemotherapy remains unknown in this regard for the time being.

As shown in Table 2, the seven patients who survived the first 3 weeks all responded. Furthermore four of the seven patients obtained a CR in the brain. A considerable effect was demonstrated in the partial responders as well. Patient No. 3, who started out with >15 lesions at the CT scan, had only two remaining lesions at 3 months re-scan. At the eventual systemic relapse, these two initially stationary brain lesions progressed concomitantly with lesions in the lung, liver and skin.

Similarly, patient No. 5 had one remaining brain tumor at 3 months evaluation out of the initial five. At autopsy, shortly thereafter, the remaining occipital tumor was the only malignant tissue left in this patient, who died of bronchopneumonia. The histology of the brain tumor was, as in the initial mediastinal biopsy, SCLC. Patient No. 6 obtained a CR both in the CNS and peripherally, but contracted a fatal pneumonia and septicemia. The CR was confirmed at *post mortem*, which demonstrated no remaining tumor, including a detailed microscopical examination of the brain.

DISCUSSION

This study includes all SCLC patients with initial brain metastases, treated with chemotherapy as the sole primary treatment, during the past 18 months at the Finsen Institute.

The data from the present study suggests that combination chemotherapy, including drugs such as alkylating agents, nitrosureas, epipodophyllotoxins, vincristine and cisplatinum, has as pronounced an initial effect on metastatic small cell carcinoma in the brain as is observed in other peripheral organs in patients with SCLC.

The results are not in accordance with the concept of the blood–brain barrier (BBB) allowing only highly lipophilic substances to enter the brain tumor parenchyma. Drug penetration of normal brain

endothelium is mediated by simple diffusion [13, 14] and is ultimately limited by several factors. These are the solubility of the compound in plasma, its protein binding, ionization, clearance and, if lipophilic, its entrapment in lipid compartments [14]. The cisplatin concentration in the CSF is low following intravenous administration in humans [15] without brain metastases as well as in normal monkeys [16]. In patients with primary germ cell tumors of the brain CSF cisplatinum levels temporarily exceeding those of plasma has been demonstrated [17], as well as excellent responses [6]. In the latter series of 10 patients with germ cell tumors in the brain, intrathecal methotrexate, however, was also given. The relative influence of the latter compound is unknown but, according to Greig [14], brain penetration of antineoplastic agents from the CSF is minimal.

Laborious attempts to modify the impact of the BBB, including various chemical substances, hyperosmotic agents, physiological approaches and even microwaves, have been introduced, at present not yielding affirmative results [5, 18].

A simple clinical trial testing the effect of systemic chemotherapy vs. chemotherapy plus radiation on primary metastatic brain tumors in consecutive unselected patients with SCLC has not yet been performed. Cranial irradiation probably affects the capillary integrity in brain parenchyma [19, 20], suggesting an advantage of combined treatment compared to single modality treatment. This may explain the relatively good prognosis of initial brain metastases in SCLC, compared to CNS metastases at relapse. On the other hand, the same synergism is presumed to cause increased toxicity, making the brain more susceptible to neurotoxic cytostatic agents when concomitant radiation is applied [21].

For this reason it cannot be excluded that the influence on the CNS of radiotherapy may aggravate the adverse impact of brain metastases on the patients quality of life.

The aim of the present report is to document the response of brain metastases from SCLC to systemic combination chemotherapy. It is too early to evaluate the impact of this observation on the overall strategy of the treatment of SCLC as further quantitative data concerning overall survival, and toxicity, including quality of life, requires inclusion of larger groups of patients preferably in prospective randomized studies.

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