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Treatment of Brain Metastases of Lung Cancer with High Doses of Etoposide (VP16–213). Cooperative Study from the Groupe Français Pneumo-Cancérologie

J. P. KLEISBAUER,* D. VESCO,* J. OREHEK,* B. BLAIVE,† C. CLARY,† R. POIRIER,‡ S. SARETTO,‡ P. CARLES,§ G. DONGAY,§ J. C. GUERIN‖ and Y. MARTINAT‖

*Hôpital Salvator, 249, Bd de Sainte-Marguerite, Marseille, †Hôpital Pasteur, Avenue de la Voie Romaine, Nice, ‡Centre Hospitalier, Avenue des Tamaris, Aix-en-Provence, §Hôpital Purpan, Place du Docteur Baylac, Toulouse and ‖Hôpital de La Croix Rousse, Lyon, France

Abstract—*To study the efficacy of etoposide in brain metastases of lung carcinoma, etoposide was given during* 3 *consecutive days. The total dose of* 1500 mg/m^2 *was divided into six* 1 h *perfusions delivered over* 3 *days to* 19 *patients having squamous* (7), *large cell* (3), *small cell* (5) *or adenocarcioma* (4). *Response to chemotherapy was assessed by means of computerized tomography (CT) before and* 15–30 *days after the last course of chemotherapy (course interval* = 28 *days, maximum of four courses).*

Severe myelotoxicity was observed in nine patients with seven patient deaths resulting from infection.

Efficacy could be evaluated in 13 *patients. Failure was observed in seven cases. An objective response was observed in six patients* (4/14 *NSCLC and* 2/5 *SCLC), two patients having a complete regression. Average survival time was* 10 *weeks.*

INTRODUCTION

ETOPOSIDE (VP 16-213) is a fairly new antineoplastic agent with proven efficacy against lung carcinoma. Toxic effects include myelosuppression, alopecia, stomatitis, nausea, vomiting, fever and peripheral neuropathies [1, 2]. The recommended dose is 300 mg/m^2, although much higher doses have been used in combination with autologous bone marrow transplantation [3]. Hepatic injury is also a potential complication of high dose therapy [4]. A dose of 2400 mg/m^2 resulted in severe mucositis in 11% of patients. This dose was thus defined as the maximally tolerated dose in terms of extra medullary toxicity [3]. Doses of etoposide up to 1500 mg/m^2 lead to severe, but reversible, myelosuppression, whereas extramedullary toxicity was minor, making it an acceptable dose for clinical use [5]. In another study [6], the dose limiting toxicity of high dose etoposide, administered i.v. on 3 consecutive days, was oropharyngeal mucositis, occurring at 3.5 mg/m^2; the hematologic toxicity was severe but not dose dependent. High doses of etoposide (between 0.9 and 2.5 g/m^2) have been administered to patients suffering from central nervous system metastases of small cell lung cancer (SCLC) while the levels of VP 16-213 in plasma and cerebrospinal fluid were compared [7]. The data showed that the drug crossed the blood–brain barrier in small amounts and was clinically effective on two patients.

Preliminary data [8] suggested that high dose etoposide was effective in brain metasases of lung cancer. The purpose of the present study was to further investigate the efficacy of etoposide in brain metastases of non small cell lung cancer (NSCLC) and SCLC.

METHODS

Chemotherapy

Etoposide (Vepesid Sandoz Laboratory) was given to all patients, during 3 consecutive days, the total dose of 1500 mg/m^2 being divided into six 1 h perfusions, at 12 h intervals.

Etoposide was dissolved in normal saline with a

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Correspondence and reprint requests: Docteur J. P. Kleisbauer at above addresss.

Table 1

Patient number	Age	Pathology	Chemotherapy Previous	Chemotherapy With VP	Number of courses	Efficacy toxicity	Cranial radiotherapy after chemotherapy	Survival (weeks)
1	53	Adenocarcinoma	No		3	CR	Yes	32
2	57	Adenocarcinoma	No		1	IT4	No	5
3	48	Adenocarcinoma	Yes	No	2	PR	No	10
4	74	Squamous	No		2	PR + IT4	No	8
5	72	Large cell	Yes	Yes	1	IT4	No	2
6	70	Squamous	Yes	No	2	P	No	11
7	73	Adenocarcinoma	No		1	IT4	No	2
8	53	Small cell	Yes	Yes	3	PR + IT3	Yes	40
9	55	Squamous	Yes	Yes	2	P	No	5
10	59	Squamous	No		1	IT4	No	2
11	63	Small cell	Yes	Yes	4	PR	Yes	34
12	55	Squamous	No		1	P	No	2
13	50	Small cell	Yes	Yes	2	P	Yes	32
14	52	Squamous	Yes	Yes	2	P	Yes	16
15	55	Large cell	No		2	P	No	13
16	57	Small cell	Yes	Yes	1	IT4	No	2
17	73	Squamous	No		1	IT4	No	2
18	45	Small cell	Yes	Yes	1	P	No	12
19	68	Large cell	No		2	CR	Yes	16

CR = Complete response, PR = partial response, P = progression, IT3 = major toxicity, IT4 = death.

maximum concentration of 0.8 mg/ml. The total dose for one course varied from 2400 to 3000 mg. The number of courses varied from one to four (Table 1). Each course was done every 4 weeks. At new course treatment was postponed for one week when platelets counts was found below 100,000 or leucocytes below 2×10^3. During the first course of chemotherapy the patients received Synacthen®, 1 mg/day during 3 days and 1 mg every 2 days for the remainder of the first 4 weeks. Thereafter, no polypeptide therapy was used.

Patients

Nineteen consecutive patients (1 female, age range 45–74 years), who were followed from January 1985 to October 1985, have been included in this study.

All suffered from lung carcinoma diagnosed by endoscopy and biopsy (small cell 5, adenocarcinoma 4, squamous 7, large cell 3).

Nine patients had not been treated with chemotherapy before, the other 10 had received one or more courses of various chemotherapies. In some cases ($n = 8$) etoposide had been administered previously at a less dose (300 mg/m^2). No patient had had prior cranial radiation therapy (Table 1).

Evaluation of response

Efficacy was assessed by means of CT scan 15–30 days after the last course of chemotherapy. Detection of brain metastasis was performed by CT scan with injection of Telebrix®. Objective response was defined as a reduction of more than half of the two crossing diameters on the same slide (Figs 1 and 2). Toxicity grading was done according to WHO criteria. Major toxicity or lack of efficacy after two to three courses led to a change in therapy. Radiotherapy was performed after appreciation of the efficacy of the drug. No measures were taken against infection. No prophylactic antibiotic therapy was given to prevent infection.

RESULTS

Severe myelotoxicity (anemia, leucocyte counts less than 1000 and platelet counts less than 10,000) occurred between the 7th and the 12th days after the first course of chemotherapy in six patients, after the second course in one patient and after the third course in two patients. Seven patients died from infection.

Response was evaluated in only 13 patients who survived more than 4 weeks and had more than one CT scan.

Failure was observed in seven cases. Objective responses occurred in six patients with partial response in four cases and total response in two. One of these two patients relapsed within 5 weeks while the other one was free from disease for 8 months.

Partial response (PR) and complete response (CR) were achieved in: one squamous cell tumor (1 PR); two adenocarcinoma (1 PR, 1 CR); one large cell carcinoma (1 CR); two small cell carcinoma (2 PR).

Objective response was achieved in three of nine patients never treated before with chemotherapy, in one out of two patients treated before without etoposide and in two out of eight patients treated before with etoposide. Survival of more than 3

Patient No. 8
CHA. . . Small cell carcinoma

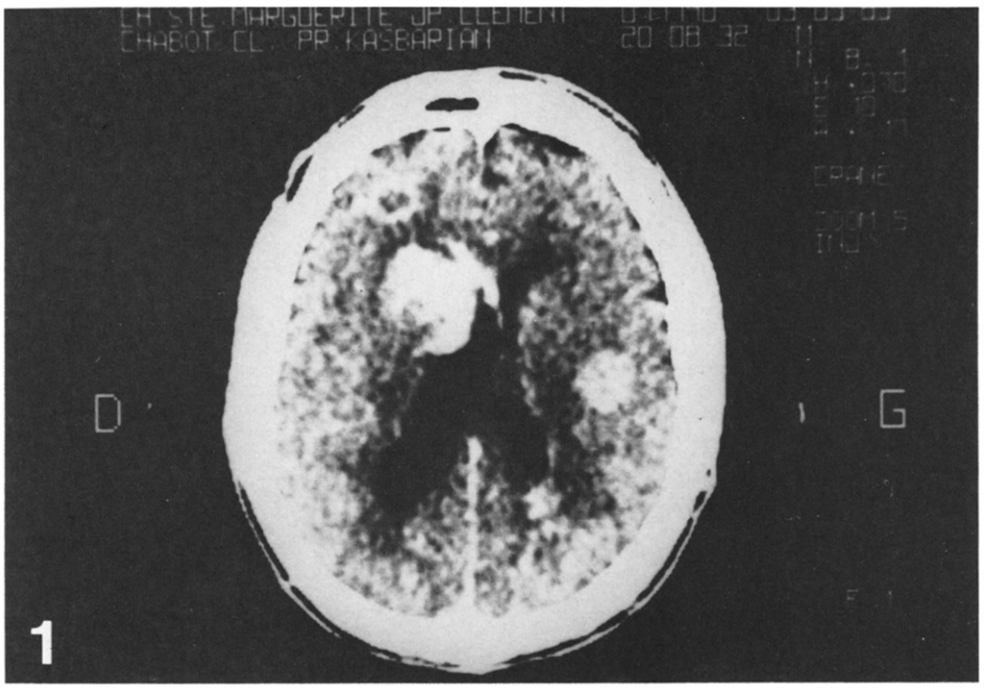

Fig. 1. *Cerebral CT scan before chemotherapy.*

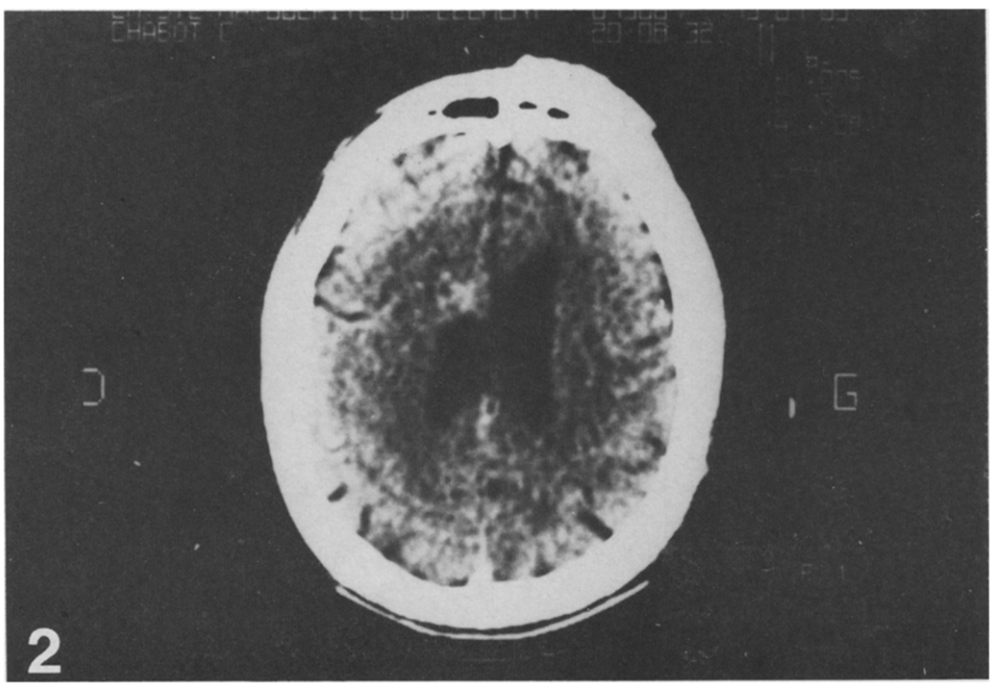

Fig. 2. *Same patient after three courses of VP* 16. *Partial remission.*

months was observed in the two patients with complete response (16 and 32 weeks), in two of the three partial responses (34 and 40 weeks) and in two non-responders with radiotherapy afterwards (16 and 32 weeks).

DISCUSSION

With similar doses of etoposide, Postmus *et al.* reported objective responses in two out of 10 patients with central nervous system metastases of SCLC [6], despite the fact that penetration of etoposide into the cerebrospinal fluid was low (about 1% of the serum level).

The present data indicate that high doses of etoposide can cause partial or complete regression of brain metastases from SCLC but also from NSCLC which are reputed to be less sensitive than SCLC to this antineoplastic agent. The percentage of objective response was about 30%, and it was similar in NSCLC and SCLC, but the numbers are too small to have statistical significance. Clinically, objective response on CT scan corresponded to an improvement in the neurological symptoms.

Objective responses were observed in some patients who had been treated before with chemotherapy (3/10) as well as in some who had never been treated before (3/9). Two patients out of eight who had previously received etoposide were responders. However, we could not relate the efficiency at the lung site to the efficiency at the brain site because the number of patients who had never been treated before on the lung site was too small.

Objective responses were obtained at the cost of seven treatment-related deaths. Furthermore, four of the six patients having a remission had died at the end of 10 months. Thus it seems doubtful that treatment with such doses of etoposide is clinically justified. However, future studies with smaller doses might be worthwhile in the hope of retaining the beneficial effects on the brain tumors while decreasing the side-effects. The rather high incidence of remission obtained in this study is surprising since the level of etoposide in the cerebrospinal fluid is only 1% of that in the serum [7]. Presumably the explanation is that etoposide passes from blood to tumoral tissues but not from blood to cerebrospinal fluid.

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