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Phase I Study of a Carboplatin–Etoposide Combination in Advanced Thoracic Cancer

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Abstract—*We conducted a phase I trial with the combination carboplatin (CBDCA)–etoposide (VP-16) in thoracic cancer. CBDCA, at a starting dose of 300 mg/m² d1, was associated with a fixed dose of VP-16 (100 mg/m² d1–3). Escalation of doses was permitted after three patients entered at each dose level without grade IV toxicity. As expected, hematologic toxicity was the limiting factor. Severe myelosuppression (grade IV) occurred in three out of four patients treated at 350 mg/m². Only three out of 19 patients treated at 325 mg/m² exhibited a reversible grade IV hematologic toxicity. Other toxicities were mild and acceptable. Among 15 evaluable patients three showed a partial response. Two of the three responders have previously had a progression while receiving cisplatin and etoposide.*

The recommended dose of carboplatin to be associated with VP-16 (100 mg/m² d1–3) is thus 325 mg/m² d1.

INTRODUCTION

THE ROLE of chemotherapy in the management of non-small cell lung cancer (NSCLC) remains controversial, since, so far, it has been associated with a relatively low response rate and no major improvement of overall survival [1–3]. In the experience of the EORTC Lung Cancer Working Party, a high dose of cisplatin (120 mg/m²) induced a 26% rate of objective responses in NSCLC [4]; combination therapy with cisplatin (DDP) (60 mg/m²) and etoposide (VP-16) [5] resulted in a 38% response rate, but the use of a higher dose of cisplatin (120 mg/m²) in combination with VP-16, did not result in a significantly higher response rate than a lower dose (60 mg/m²) [6].

Carboplatin (paraplatin, JM8, CBDCA or *cis*-diammine-1,1-cyclobutane dicarboxylate platinum II) is a platinum derivative which appears to be less toxic than cisplatin both in animal [7] and human studies [8, 9]. Moreover, there is some evidence of non-cross resistance with cisplatin in ovarian cancer [10].

Preliminary studies reported activity of CBDCA in patients with NSCLC [11] although it appeared more active in small cell lung cancer (SCLC) [11–13]. Other studies have shown that CBDCA (300 mg/m² d1) can be combined to VP-16 (100 mg/m² d1–3) with acceptable toxicity in SCLC [14]. Lower doses of CBDCA (100 mg/m² d1) with VP–16 (120 mg/m² d1–3), yielded a 66% objective response rate in SCLC [15].

The aim of this phase I trial was to determine the optimal dosage of carboplatin (d1), in association to a fixed dose of etoposide (100 mg/m² d1–3) in thoracic cancer.

PATIENTS AND METHODS

Patients with unresectable, histologically proven lung cancer or mesothelioma were eligible. Patients with prior therapy had to be off any anticancer treatment for at least 4 weeks; a performance status of at least 60 on the Karnofsky scale or/and life expectancy of at least 2 months were required. The serum creatinine had to be lower than 1.5 mg/dl and/or the creatinine clearance superior to 60 ml/min. The patients had to have a WBC count >4000/mm³, platelet count >100,000/mm³; to be free of infection, of congestive heart failure or cardiac arrhythmias requiring medical treatment; to have no myocardial infarction history within the 3 months prior to diagnosis; to have serum bilirubin <1.5 mg/dl. Patients had to give informed consent to participate to the study that was approved by the ethical committee of our institution.

Chemotherapy was administered every 4 weeks. The starting dose of CBDCA was 300 mg/m² i.v. d1, followed by VP-16 (100 mg/m² d1–3). A minimum of three patients were treated at each dose

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level. If no major toxicity occurred, the dosage of CBDCA was increased by step of 25 mg/m^2, until repeated WHO grade toxicity occurred. Then, the previous dose level was considered as the maximum tolerated dose and additional patients had to be treated at this dosage in order to assess the toxicity of this optimal dose level. Tumor response was evaluated after three courses of chemotherapy unless there was evidence of earlier progression. Responding patients were continued on therapy until progression or no further response during two successive courses.

CBDCA (supplied by Bristol-Myers), was diluted in 500 ml of glucose 5% and infused over 60 min. VP-16 was diluted in 500 ml of 0.9% saline and infused over 60 min on days 1, 2 and 3. High dose metoclopramide (2 mg/kg) was administered before and after administration of chemotherapy.

If the WBC count was <4000/mm^3 and/or the platelet count <150,000/ml, the treatment was postponed for 1 week. If the treatment had to be postponed for more than 2 weeks, the patient went off study. If the platelet nadir was between 20,000 and 50,000/mm^3, both drugs were administered at 75% of the initial dose. If the platelet nadir was <20,000/mm^3, 50% of the doses of CBDCA and VP-16 were given. Finally, if the serum creatinine level was between 1.5 and 3 mg/dl, only the dose of CBDCA was reduced to 50%; if the creatinine level was above 3 mg/dl, the treatment was discontinued.

Toxicity was evaluated according to the WHO grading system. Partial response was defined as a ≥50% decrease of the sum of the products of bidimensional diameters of measurable lesions. Progression was defined as a ≥25% increase of the sum of the products of these diameters or the occurrence of any new lesions.

The patient was considered as evaluable if he completed three courses of treatment. Deaths due to progression of disease prior to the evaluation of response were considered as early deaths. Toxic deaths were those that could be attributed to toxicity of chemotherapy.

RESULTS

Most patients had non-small cell lung cancer (NSCLC), either adenocarcinoma, squamous cell carcinoma or large cell carcinoma. Three patients with a small cell lung cancer (SCLC), one patient with an undifferentiated tumor and three with mesothelioma were also included. Over an 8 month period, 25 patients were studied; four had no prior therapy and 21 had received prior treatment with chemotherapy and/or irradiation. The characteristics of these patients including age, sex, performance status, histology and extension of tumor are given in Table 1.

The mean number of cycles administered was 2.5 (range 1–7). Twenty-three of 25 patients were evaluable for toxicity; Table 2 summarizes the previous treatments received by the patients as well as the corresponding dose of CBDCA administered, the hematologic toxicity and the response observed. Out of the 17 patients who received prior chemotherapy, 14 were previously treated with VP-16 alone or in combination with other drug and 10 patients were treated with regimen including DDP and VP-16. As expected, reversible myelosuppression during CBDCA escalation was the major toxic effect. Severe pancytopenia (grade III–IV), neutropenia and/or thrombocytopenia were documented in three of the four patients treated with 350 mg/m^2 of CBDCA. Two of these patients had not received prior chemotherapy. Twelve more patients were treated at 325 mg/m^2 and 3/15 had grade IV hematologic toxicity at this level (Table 2). Five patients treated at 325 mg/m^2 of CBDCA required a blood transfusion because of anemia. Grade III alopecia occurred in five patients. Grade III nausea and vomiting occurred in five patients; two patients at 300 mg/m^2 and three patients at 325 mg/m^2 of CBDCA. A patient had anaphylaxis caused by VP-16 and the drug was discontinued. Two patients were not evaluable for toxicity; one because of early death and the other refused the scheduled controls.

In 19 patients, the efficacy of therapy could be evaluated. Two were not evaluable for response because of early death unrelated to cancer and four because of lack of evaluable lesion. Three achieved a partial response; two of them were *resistant* to a previous treatment with cisplatin and etoposide. Five patients had a stable disease during therapy with CBDCA and VP-16 and the tumor progressed in 11 patients (Table 3).

All responding patients presented with a disseminated (measurable) disease and all had previously received radio- and chemotherapy. One (SCLC) died after 29 weeks, still in partial remission; the two other patients (NSCLC) are still alive but both showed a progression 24 weeks after the onset of the treatment (Table 4).

DISCUSSION

Advanced lung cancer is still a highly fatal disease since presently available chemotherapy has no major influence on the survival. It is therefore important to investigate new drugs and novel therapeutic modalities in order to improve the present results of chemotherapy. CBDCA alone has shown some activity in lung cancer, particularly in SCLC; the combination CBDCA plus VP-16 has been evaluated in SCLC. Since cisplatin and VP-16 in combination have some activity in NSCLC, it was quite logical to investigate CBDCA (which is less

Table 1. Patient characteristics

Number of patients	25
Median age in years (range)	57 (40–74)
Median PS (Karnofsky)	70 [60/90 (2 unknown)]
Sex: males/females	19/6
Median loss of body weight	8 [0–50% (4 unknown)]
Disease extent:	
locoregional	5
disseminated	20
Histology:	
squamous cell	6
adenocarcinoma	8
large cell	4
small cell	3
mesothelioma	3
other	1
Prior treatment:	
none	4
radiotherapy	4
chemotherapy	6
radiotherapy + chemotherapy	11
Disease:	
evaluable	15
measurable	9
not evaluable	1

Table 2. Hematologic toxicity and treatments received

Dose of carboplatin	Previous therapy		Patients	Hematologic toxicity (grades)		Response
	CT	RT		WBC	Platelets	
300 mg/m²	+ DDP	+	1	III	III	NC
	+ DDP–VP16	+	2	0	0	PR
	0	+	3	Not evaluable		ED
	0	0	4	I	0	PD
	0	0	5	I	0	NC
325 mg/m²	+ MOPP*	+	6	II	0	PR
	+ 6-aminochrysene	0	7	II	0	NC
	0	+	8	II	0	NE
	+ VDS/DDP–VP16	0	9	0	0	NE
	+ DDP–VP16	0	10	III	III	PD
	+ DDP–VP16	+	11	II	II	NE
	+ DDP–VP16	+	12	IV	III	NC
	0	0	13	I	0	PD
	+ DDP	+	14	II	II	PD
	+ DDP	+	15	I	0	PD
	+ VAC/DDP–VP16	0	16	I	IV	NE
	+ DDP-VP16	+	17	0	0	PD
	+ CAVE	+	18	III	II	PD
	+ CPA–CCNU–MTX/ DDP–ADM–VP16	+	19	IV	III	PR
	+ DDP	0	20	II	0	PD
350 mg/m²	+ AVE	0	21	II	0	PD
	0	+	22	IV	IV	ED
	+ DDP–VP16 CAVi–6-aminochrysene	+	23	III	IV	PD
	0	+	24	IV	III	NC
	0	0	25	Not evaluable		PD

DDP (cisplatin); VDS (vindesine); VP-16 (etoposide); CPA (cyclophosphamide); ADM (adriamycin); CCNU (lomustine); MTX (methotrexate); MOPP (cyclophosphamide, vincristine, procarbazine, prednisone); VAC (vincristine, adriamycin, vincristine, etoposide); CAVi (cyclophosphamide, adriamycin, vincristine); AVE (adriamycin, vincristine, etoposide); NC: no change; PR: partial response; PD: progressive disease; NE: not evaluable; ED: early death.

*Administered for a Hodgkin disease 10 years before.

nephro- and neurotoxic) instead of cisplatin in combination with VP-16.

Preliminary phase I trials have recommended a maximal dose of CBDCA in the range of 400 to 500 mg/m^2, that could be administered repeatedly, without excessive myelosuppression [7]; only above 450 mg/m^2 was nephrotoxicity observed [16]. In combination with other myelosuppressive agents, the CBDCA dose had to be reduced. According to our results, the optimal recommended schedule for phase II trials is the following: CBDCA (325 mg/m^2 d1) and VP-16 (100 mg/m^2 d1-3), to be repeated every 4 weeks.

The results of the present study confirm some activity of the combination of CBDCA + VP-16 in NSCLC: 3/19 patients had a partial response, although most of them had been previously heavily treated with chemotherapy and/or radiotherapy.

Table 3. Evaluation of response

Registered patients	25
Evaluable for response	19
Partial response	3*
Stable disease	5
Progression	11
Early death	2
Toxic death	0

*Including two after progression during chemotherapy with cisplatin + etoposide.

Our study also suggests that, in lung cancer, and this has already been shown in ovarian carcinoma, there might not be a complete cross-resistance between cisplatin and carboplatin, since two out of the three responding patients in this study had previously failed to respond to cisplatin–VP-16.

Table 4. Characteristics of responding patients

	1	2	3
Age	70	70	57
Sex	Male	Male	Male
Performance status (Karnofsky)	90	60	90
Loss of weight (%)	0	5	4
Extension of disease	Disseminated	Disseminated	Disseminated
Histology	Large cell carcinoma	Small cell carcinoma	Squamous cell carcinoma
Previous treatment	Radiotherapy + chemotherapy*	Radiotherapy + chemotherapy†	Radiotherapy + chemotherapy‡
Carboplatin dose	300 mg/m^2	325 mg/m^2	325 mg/m^2
Survival	26 weeks§	29 weeks	54 weeks§
Time to progression	24 weeks	24 weeks	24 weeks

*DDP-VP16.
†CPA–CCNU–MTX/DDP–ADM-VP16.
‡MOPP.
§Still alive.

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