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A Phase II Study of 4'-Epi-Doxorubicin plus *Cis*-Platinum in Advanced Solid Tumors

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Abstract—*4'-Epi-doxorubicin (4'-epi-DX) is a new doxorubicin derivative that in phase II human studies has been demonstrated to be less toxic than doxorubicin. Sixty-four patients with advanced solid tumors were treated with the drug combination of 4'-epi-DX and cis-dichlorodiammineplatinum (CDDP) at the doses of 40–60 and 50 mg/m², respectively, every 21–28 days. Out of 52 evaluable patients, complete remission (CR) was recorded in 5, partial remission (PR) in 12, minor remission (MR) in 7, no change (NC) in 16 and progression (P) in 12. The median duration of remission in patients who achieved a CR and PR was 9+ months. In particular, out of 19 patients with ovarian cancer, 2 CR (second look) and 7 PR have been documented. One CR and 3 PR also have been observed in 21 patients with lung carcinoma. Complete and partial responses also have been documented in breast cancer (1 CR/1), in bladder carcinoma (1 CR/2), in renal cancer (1 PR/5) and in testicular cancer (1 PR/1). Hematologic toxicity was generally mild to moderate (leukopenia ≤1500 cells/mm³ in 3% of the patients; thrombocytopenia ≤120,000 cells/mm³ in 2% of the patients). Vomiting was present in almost all patients while alopecia has been recorded in 63% of the patients. No case of cardiac toxicity had been observed up to now (median cumulative dose of 4'-epi-DX: 240 mg/m², range 40–650 mg/m²). The combination of 4'-epi-DX with CDDP appears to be an active and well-tolerated regimen in ovarian cancer and lung cancer.*

INTRODUCTION

4'-EPI-DOXORUBICIN (4'-epi-DX) is a new doxorubicin (DX) derivative which in preclinical studies has been shown to possess a better therapeutic index and in particular less cardiac toxicity [1]. Phase I and II human studies [2–6] also confirmed that myelosuppression, vomiting, alopecia and stomatitis were less severe than with comparable doses of DX. In a recent phase II study with 4'-epi-DX (90 mg/m²) carried out in our Institution [5], we observed a pattern of toxicity similar to that of DX, but the intensity and frequency of hematologic toxicity and vomiting were lower than those recorded with DX (80 mg/m²) [7].

4'-Epi-DX is characterized by a different pharmacokinetic behaviour as compared to DX, mainly consisting of a faster metabolization and elimination processes [8, 9], and this finding could be correlated with the observation of the lower acute and chronic toxicity found in clinical testing.

In our previous phase II study [5, 10], 4'-epi-DX has shown activity in breast cancer, ovarian cancer, lung cancer and gastric cancer. For these reasons, a phase II trial of 4'-epi-DX in combination with *cis*-dichlorodiammineplatinum (CDDP) was initiated in patients with diseases (mainly ovarian cancer and lung cancer) which are known to be responsive to DX and/or CDDP in order to define activity and toxicity of this combination regimen.

MATERIALS AND METHODS

Sixty-four patients with histologically proven, measurable and/or evaluable advanced solid tumors not amenable to surgery and/or radiation therapy were entered in the study. Some of the main characteristics of the patients are listed in

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Table 1. Six out of 24 patients with lung cancer had been previously treated with radiation therapy (mediastinal irradiation <4000 rad); 9 out of 23 patients with ovarian cancer had been previously treated with chemotherapy and/or radiation therapy; 2 patients with testicular cancer and one with breast cancer had been previously treated with chemotherapy; patients with renal cancer and head and neck cancer had not been previously treated with chemotherapy. Furthermore, 4 patients did receive previous DX at a total dose of $\leqslant 250$ mg/m^2.

Patients were excluded from the study if they were >75 years old, if they had a Karnofsky performance status <30, life expectancy <2 months, WBC count <4000/mm^3, platelet count <100,000/mm^3, or bilirubin >1.5 mg% and creatininemia >1.5 mg%; if there was evidence of congestive heart failure or if they had cardiac ischemia or arrhythmia.

4'-Epi-DX was administered at three different dose levels: 13 patients received 40 mg/m^2, 11 patients received 50 mg/m^2 and 40 patients received 60 mg/m^2. In no case was there escalation of the initial dose. CDDP was always administered at 50 mg/m^2. Figure 1 shows the scheme of treatment.

4'-Epi-DX, supplied by Farmitalia Carlo-Erba S.p.a. in 10 and 50 mg vials, was reconstituted with sterile water for injection and administered in 5 min into the tubing of a rapidly flowing i.v. infusion of normal saline solution. After 1 hr CDDP by i.v. bolus was administered. A 2 hr hydration with forced diuresis by furosemide and

Table 1. Patient characteristics

Total No. of patients	64
Male	34
Female	30
Age (yr)	
Median	54
(Range)	(25–72)
Performance status (Karnofsky)	
Median	60
(Range)	(30–100)
Primary tumors (No.)	
Lung	24
Ovary	23
Kidney	6
Cervix	4
Testicle	2
Bladder	2
Head and neck	2
Breast	1
Prior therapy (No.)	
Radiation	22
Chemotherapy	23
Hormonal	10
Doxorubicin	4
(total cumulative dose $\leqslant 250$ mg/m^2)	

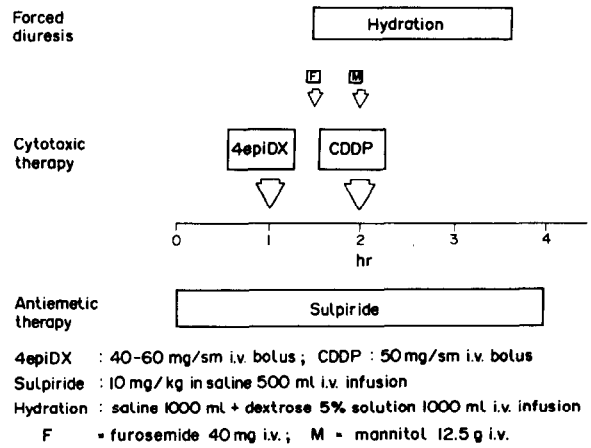

Fig. 1. Scheme of treatment.

mannitol was done according to Vogl [11]. As antiemetic supportive treatment we administered sulpiride (10 mg/kg by 4 hr infusion), a drug which in our previous experience has shown to be useful in controlling vomiting induced by CDDP [12]. Both 4'-epi-DX and CDDP were administered on day 1 and each subsequent treatment cycle was repeated at 3–4 week intervals. The treatment was considered adequate for objective response after a minimum of 2 cycles of drugs. After 2 cycles, in absence of progression, the treatment was continued until disease progression or severe toxicity. A total cumulative dose of 4'-epi-DX exceeded 500–540 mg/m^2 only in the absence of cardiac toxicity assessed by a complete cardiac evaluation including ECG, radionuclide angiography and/or phonocardiography.

Studies obtained prior to initial therapy consisted of medical history, physical examination with measurement of indicator lesions, chest roentgenogram, metastatic bone survey, echography, ECG and left ventricular ejection fraction (EF) by means of radionuclide angiography. Clinical examination was repeated prior to each subsequent treatment while instrumental assessment was made every 2–3 courses. A full blood count, serum electrophoretic pattern, alkaline phosphatase, bilirubin, SGOT, SGPT, BUN and creatinine were done at the start of treatment and at regular intervals thereafter (once or twice a week and in each case before the next course).

A complete response (CR) was defined as the disappearance of all evidence of tumor lesions for at least 6 months. A partial response (PR) was defined as a $\geqslant 50\%$ decrease of the sum of the product of the longest perpendicular diameters of all measurable lesions and/or evident and unquestionable decrease of evaluable but not measurable tumor lesions. A minor response (MR) was defined as a >25% but <50% decrease of all measurable lesions. Stabilization (NC) was

defined as a stationary condition of measurable and/or evaluable lesions, while disease progression (P) was defined as the widening of the surface even of one lesion only, by >25% or the appearance of a new metastatic lesion.

RESULTS

Out of 64 patients, 7 received only 1 cycle of treatment, 10 received 2 cycles, and 47 received more than 2 cycles (median: 5 cycles, range: 1–13).

Median cumulative dose of 4'-epi-DX and CDDP was, respectively, 240 and 250 mg/m^2; in 5 patients the total dose of 4'-epi-DX exceeded 500 mg/m^2 (Table 2). Twenty-three patients are still on treatment.

Table 2. Cumulative doses

mg/m^2	4'-Epi-DX (No. of patients)	CDDP (No. of patients)
≤100	10	17
101–200	19	14
201–300	13	16
301–400	9	10
401–500	8	4
>500	5	3
Median	240	250
(Range)	(40–650)	(50–650)

Therapeutic effects

Fifty-two of the 64 patients who entered the study are evaluable for therapeutic effect. Twelve were not considered evaluable for the following reasons: 6 patients demonstrated marked disease progression before the second dose was administered; in 2 patients protocol violations were present; another patient refused a second dose after experiencing severe vomiting; 3 patients with non-measurable stage III ovarian cancer were not yet evaluable for response, the 'second look' laparotomy still to be performed. The response is shown in Table 3. CR was achieved in 5 (10%) patients: 2 patients had peritoneal carcinosis secondary to ovarian cancer and in both a 'second look' laparotomy performed after 7 and 8 courses of therapy, respectively, did not show any macroscopic neoplastic lesions. The other 3 CR were achieved in 1 patient with small cell lung cancer, in 1 patient with a locally recurrent bladder cancer, and in 1 patient with supraclavicular and retroperitoneal metastatic lymphonodes from breast cancer. This last patient, who had previously received radiation therapy and 6 courses adjuvant CMF, experienced a prolonged leukopenia after the first course of therapy which has precluded further treatment, but she is still in complete remission after 13 months.

PR was achieved in 12 (23%) patients: 7 patients with advanced ovarian carcinoma, 3 patients with epidermoid lung cancer, 1 patient with renal cancer and 1 patient with testicular cancer. In another 7 (13%) patients an MR was obtained: 4 patients with lung cancer and 3 with ovarian cancer.

The response in 21 evaluable lung cancer patients according to the histological subtype was the following: epidermoid (7): 3 PR, 3 NC, 1 P; adenocarcinoma (7): 2 MR, 3 NC, 2 P; small cell anaplastic (4); 1 CR, 2 MR, 1 P; large cell anaplastic (3): 3 NC. CR and PR was achieved only in non-pretreated patients. Among pre-irradiated patients 2 out of 6 achieved MR. Analyzing objective response in ovarian cancer according to prior treatments, CR and PR was observed in 5/11 (45%) previously untreated patients and in 4/8 (50%) patients previously treated with chemotherapy (alkylating agents or multidrug regimens containing DX).

Median duration of CR and PR was 9+ months, whereas for the MR it was 6 months. Up to the present date all the patients who experienced a CR are relapse free; recurrence of disease occurred in 5 out of the 12 patients who had a PR and in 4 out of the 7 who had an MR. As far as ovarian cancer is concerned only 1 patient out of 9 who experienced CR or PR and 2 out of 3 who had an MR relapsed. The median survival time of the patients with lung cancer is 7+ months, without any difference between responders and non-responders. The median survival time of the patients with ovarian cancer is 9+ months: for the responders the median survival is 10.5 months and for non-responders is 5 months.

Toxic effects

The hematologic toxicity encountered during treatment is reported in Table 4. Leukopenia with WBC counts ≤3000/mm^3 was seen in 51% of the patients, and with WBC counts ≤1500/mm^3 in 3%. Thrombocytopenia was uncommon: 28% of the patients had a platelet count nadir >80,000/mm^3, and 2% had a nadir ≤80,000/mm^3. Out of a total of 307 courses administered, leukopenia was observed in 30% and thrombocytopenia in 8%. The median nadir after the first course with the dose of 60 mg/m^2 of 4'-epi-DX was 4000 WBC/mm^3 14 days after administration of the drugs, with full recovery by day 21. There were no episodes of sepsis related to marrow suppression; anemia was uncommon, 11% of the patients experiencing ≤8% of Hb. Other side effects (Table 5) included vomiting in almost all patients; out of a total of 307 courses administered, vomiting was observed in 86%, starting within 1–2 hr after CDDP and lasting an average of 2 hr. Alopecia was present in 64% of the patients, being

Table 3. Response data (52 evaluable patients)

Disease	CR	PR	MR	NC	P	Total	Not evaluable
Lung	1	3	4	9	4	21	3
Ovary	2	7	3	4	3	19	4
Kidney	0	1	0	2	2	5	1
Cervix	0	0	0	0	1	1	3
Testis	0	1	0	0	0	1	1
Bladder	1	0	0	0	1	2	-
Head and neck	0	0	0	1	1	2	-
Breast	1	0	0	0	0	1	-
Total	5(10%)	12(23%)	7(13%)	16(31%)	12(23%)	52	12

Response duration (months)	CR	PR	MR	NC
Median	9+	7+	6	5
(Range)	(8+-13+)	(3 -15+)	(3 -11+)	(2 -15+)

Table 4. Hematologic toxicity (63 evaluable patients)

	No. of patients	*
Leukopenia	46	73
Wbc (cells/mm³) 3999-3000	12	19
2999->1500	32	51
<1500	2	3
Thrombocitopenia	19	30
Platelets (cells/mm³) 120,000-80,000	18	28
≤80,000	1	2
Anemia		
Hb ≤8 g%	7	11

Table 5. Non-hematological toxicity (63 evaluable patients)

	No. of patients			
	Grade 1*	Grade 2	Total No. of patients	%
Vomiting	19	43	62	98
Alopecia	15	25	40	63
Increase in s. creatinine				
(1.6-2 mg%)	12		18	29
(2.1-2.6 mg%)		6		
Diarrhea	8	1	9	14
Fever	4		4	6
Dyspnoea	2	1	3	5
Tinnitus	2		2	3
Local	2	1	3	5
Headache	1		1	2

*Grade 1 = moderate, grade 2 = severe.

complete in about 40%. No episodes of stomatitis were noted. A transient increase of creatininemia (>1.5 mg%) was observed in 29% of the patients immediately after the first or following courses; however, only in 6 patients (10%) was this increase >2 mg% and <2.6 mg%. In 4 of the 6 patients who experienced >2 mg% increase in creatininemia, anatomical lesions of the urinary apparatus were present (three nephrectomized, and one with an obstructive urophathy from a carcinoma of the cervix). Two patients developed tinnitus, but no audiologic abnormalities were detected in the remaining patients.

Three patients with lung cancer developed dyspnoea and in one of these patients as a precaution the treatment had to be suspended after the second course in absence of ECG signs of cardiac function alteration. In the other 2 patients

the quantity of hydration liquids was reduced by 50% during the course of the subsequent treatment.

No episodes of peripheral neuropathy were noted nor signs nor symptoms of congestive heart failure, although 5 patients received >500 mg/m² of 4'-epi-DX with EF determination within the normal limits. In 12 patients radionuclide angiography was performed in basal condition and after 300–360 mg/m² of 4'-epi-DX, without cardiac alterations. In 5 out of 21 patients who received a total dose of 4'-epi-DX >360 mg/m², a decrease ⩾30% (as compared to basal values) in QRS voltage was observed, which was, however, not associated with any sign of congestive heart failure during the subsequent follow-up.

The incidence of myelosuppression and of the other acute side effects did not correlate with the three dose levels of 4'-epi-DX.

DISCUSSION

This study is the first report on the clinical experience with the combination of the new anthracycline derivative 4'-epi-DX and CDDP in the treatment of advanced solid tumors consisting mostly of ovarian carcinoma and lung carcinoma.

In pretreated advanced non-small cell lung cancer 4'-epi-DX administered as a single agent has shown up to now a low degree of activity [10, 13], while for CDDP an activity of 8% has been reported [14]. In the present study we have observed with non-small lung cancer a PR in 3 out of 17 (18%) evaluable patients and in particular in 3 out of 7 (43%) patients with epidermoid subtype; furthermore a MR has been recorded in 2 out of 7 (20%) adenocarcinomas.

From these data it appears that in non-small cell lung cancer the combination of 4'-epi-DX and CDDP is more active than the two single agents given alone. The activity of this combination regimen compares favourably with that reported for the combination of DX and CDDP [15–17] and suggests further clinical experience.

DX, CDDP and alkylating agents are first-choice drugs in first-line treatment of advanced ovarian cancer. It has been reported that the combination of DX and CDDP is able to induce an objective remission rate of 42–68% [18–20]. The response rate of 48% achieved in this study with the combination of 4'-epi-DX and CDDP appears to be encouraging since it was also obtained in patients pretreated with chemotherapy.

Other objective responses have been observed in bladder carcinoma (1 CR) and in renal cancer (1 PR). There are few and scattered data on 4'-epi-DX activity in bladder cancer, but activity of DX [21] and CDDP [22] are known. In renal cancer the preliminary activity of 4'-epi-DX [3, 10] has not been confirmed [23].

The most frequent adverse effect has been vomiting, which was recorded in almost all the patients. This is primarily due to CDDP, but 4'-epi-DX may also have enhanced this side effect. Sulpiride, as previously reported [12], can reduce intensity of vomiting but does not succeed in abolishing it.

Hematologic toxicity was relatively mild. Only in 3% and in 2% of patients was severe leukopenia (wbc ⩽1500) and thrombocytopenia (platelets ⩽80,000) observed, respectively. Previous reports of DX and CDDP administered at comparable doses indicate that the frequency and intensity of hematologic toxicity is higher than that which we have observed with 4'-epi-DX [17–19, 24]. This would confirm the lower myelosuppressive effect observed with 4'-epi-DX.

Alopecia has been recorded in 63% of patients but was total in 40% of the patients. In combination regimens containing DX and CDDP total alopecia is almost universal [17–19, 24]. The episodes of worsening renal function (measured by plasma creatinine) are in accordance with that reported for CDDP, as well as the single instances of tinnitus. The episodes of dyspnoea observed in 3 patients with lung cancer are, in our opinion, due to the amount of liquids administered to reduce the CDDP nephrotoxicity. Symptoms of congestive heart failure were not observed, although 5 patients received >500 mg/m² of 4'-epi-DX and one patient had 650 mg/m² total dose without cardiac toxicity. None of the patients had mucositis or hepatic dysfunction.

The combination of 4'-epi-DX and CDDP (60 and 50 mg/m², respectively, repeated every 21–28 days) appears in our experience to be an active regimen in the treatment of advanced ovarian and non-small cell lung cancer. Historical comparison with the results of the regimen DX and CDDP in the same diseases and at the same doses leads us to believe that the new regimen has an equivalent antitumor activity but fewer acute side effects. This result should depend on the substitution of DX with 4'-epi-DX and should confirm the better therapeutic index of 4'-epi-DX. The expansion of the study in lung and ovarian cancer will be able to verify these preliminary results and to support the substitution of DX with its new derivative.

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