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A phase-II clinical trial of 4′-epi-doxorubicin in advanced solid tumors

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Summary. *Sixty-six patients with advanced solid tumors were treated with 4′-epi-doxorubicin at a dose of 90 mg/m² by rapid IV injection every 21 days until the disease had progressed or to a maximum cumulative dose of 540 mg/m². Myelosuppression, nausea and vomiting, and alopecia were the almost frequent side effects, but their incidence seemed lower than that after a comparable dosage of doxorubicin. After a cumulative dose of 540 mg/m² a significant decrease of QRS complex deflection on the electrocardiogram was detected, but no case of congestive heart failure was observed. Partial remission and minor remission were achieved, respectively, in nine (15%) and five (9%) out of 59 evaluable patients for a median duration of 6 months. Partial remission occurred in anthracycline-sensitive tumors like breast cancer (4 of 13), lung cancer (1 of 17), head and neck cancer (1 of 8), gastric cancer (2 of 4), and ovarian cancer (1 of 1).*

Introduction

4′-Epi-doxorubicin (4′-epi-DX) is a doxorubicin (DX) analog synthetized in the Farmitalia Carlo Erba Research Laboratories [1]. Preclinical tests have found that 4′-epi-DX had the same antitumor activity as DX but less systemic toxicity and less cardiotoxicity than the parent compound [2, 6]. Initial clinical studies confirmed the results found in animals: 4′-epi-DX showed similar side effects to DX, but they were less frequent and less severe [3, 7, 11, 12]. Cardiac toxicity, evaluated by noninvasive methods and clinical observation, was also very low. Reversible acute ECG changes were observed in some treated patients, but no signs or symptoms of congestive heart failure appeared [3, 7, 13]. The present phase II clinical trial was undertaken in order to study the spectrum of antitumor activity and tolerability of 4′-epi-DX administered at the dose of 90 mg/m² in patients with malignant disease. At the same time a pharmacokinetic study was carried out [5]. The dose of 90 mg/m² was chosen on the basis of the results of the preliminary phase I study of Bonfante et al. [3]. They found the acute toxicity of 4′-epi-DX, and especially myelotoxicity, was not dose related when single doses ranging from 50 mg/m² to 90 mg/m² were used.

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Patients and methods

The study was carried out on 66 inpatients having advanced malignant refractory tumors or tumors no longer responsive to conventional cytotoxic therapies (Table 1). The criteria of eligibility were the following: likely prognosis of 2 months; performance status > 30% (according to Karnofsky); WBC count > 4,000/mm³; platelet count > 120,000/mm³; hemoglobin > 8 g/100 ml, ECG within normal limits. 4′-Epi-DX, supplied by Farmitalia Carlo Erba S.p.a. as a lyophylized powder in 10 mg and 50 mg vials, was reconstituted with sterile saline at a concentration of 2 mg/ml and was administered by IV bolus within 5 min through a running saline infusion at a dose of 90 mg/m² every 21 days until the disease had progressed and without exceeding a total cumulative dose of 540 mg/m². The dose was reduced by 30% after the first course

Table 1. Patient statistics

No. of treated patients	66
Males	33
Females	33
Age (years): median (range)	56 (22–76)
Performance status (%): median (range)	70 (40–100)
Primary tumor (no. cases)	
Lung	20
Breast	14
Head and neck	8
Stomach	4
Melanoma	4
Soft tissue sarcoma	3
Kidney	3
Endometrium	2
Ovary	1
Bladder	1
Rectum	1
Testis	1
Non-Hodgkin's lymphoma	1
Breast and stomach	1
Lung and rectum	1
Unknown	1
Previous treatments (no. of cases)	
Radiotherapy	9
Chemotherapy ± radiotherapy	32
Doxorubicin (cumulative dose < 200 mg/m²)	12

if severe side effects occurred. Before admission to the trial all patients had a physical examination, a complete blood count, a serum electrolyte test, a BUN, bilirubin, creatinine, glucose, cholesterol, total protein and albumin, SGOT, SGPT, alkaline, and acid phosphatases, urinalysis, ECG, chest X-rays, and other radiographs and scintigraphs required in relation to the disease. Patients underwent an ECG and a complete blood count twice a week after each treatment course. The cardiac ejection fraction (EF) by rest radionuclide angiocardiography in the equilibrium mode was monitored during the treatment in nine patients. In another six patients the ratio of the systolic preejection period (PEP) and left ventricular ejection time (LVET) evaluated by polygraphic standard techniques were monitored. A physical examination and biochemical analysis were repeated before each subsequent course, and instrumental assessment was made every two courses.

Complete remission was defined as the disappearance of all tumor lesions for at least 1 month. Partial remission (PR) was defined as a $\geq 50\%$ decrease in the surface (measured as the product of the longest diameter by the greatest perpendicular diameter) of all measurable lesions and/or evident and unquestionable decrease of evaluable but not measurable tumor lesions. Minor remission (MR) was defined as a $> 25\%$ and $< 50\%$ decrease in the surface of all measurable lesions. No change (NC) was defined as a $< 25\%$ change. Progression (P) was defined as a $> 25\%$ increase in the surface of only one lesion or the appearance of a new neoplastic lesion. Only patients who had received at least two courses were considered for response assessment.

Results

The dose of 90 mg/m^2 was reduced by 30% in17 patients after the first course: 15 because of severe leukopenia (WBC $< 1{,}500/\text{mm}^3$), one because of persistent diarrhea requiring therapy, and another patient because of temporary tachycardia. The median cumulative dose of 4′-epi-DX was 270 mg/m^2; 16 patients received the cumulative maximum dose of 540 mg/m^2. A list of side effects is reported in Table 2. Leukopenia was observed in 64% of patients, but only 23% had a WBC count of $< 1{,}500/\text{mm}^3$. The mean nadir value was 3,000 WBC/mm^3 on the 10th day after the first course and basal values were restored within the 20th day. The nadir and the recovery of WBC count were the same after the fourth course (Fig. 1).

Thrombocytopenia was observed in 23% of patients, but only 6% had $< 80{,}000$ platelets/mm^3. Anemia (Hb < 8 g%) was found in 11% of the patients; vomiting was transient (maximum three times) and did not require therapy. Stomatitis, diarrhea, anorexia, fever, headache, and local toxicity were rare and always mild, except for the mentioned case of diarrhea which required a reduction of the dose. There was no case with signs or symptoms of congestive heart failure. Minor and transient changes in ECG tracing (flattening of T wave, ST-T segment depression) were sporadically observed, EF determined 1, 4, 6, 24, and 32 h after the first treatment in nine patients did not show any significant changes compared to basal values (Fig. 2). Patients who received the maximum cumulative dose had a significant decrease of height of QRS complex on the ECG (Table 3), but in no case was the decrease greater than 30%. EF and PEP/LVET did not show significant changes after the cumulative dose of 360 mg/m^2 (Table 3).

Table 2. Side effects (66 evaluated patients)

	No.	%
Leukopenia	42	64
WBC $< 3{,}000 - \geq 1{,}500/\text{mm}^3$	27	41
WBC $< 1{,}500/\text{mm}^3$	15	23
Thrombocytopenia	19	29
Platelet $120{,}000 - \geq 80{,}000/\text{mm}^3$	15	23
Platelet $< 80{,}000/\text{mm}^3$	4	6
Anemia		
Hb < 8 g/100 ml	7	11
Nausea	46	70
Vomiting	41	62
Stomatitis	9	14
Anorexia	13	20
Diarrhea	6	9
Asthenia	13	20
Alopecia	43	65
Hyperpyrexia	16	24
Headache	10	15
Local toxicity	5	8
Tachycardia	1	2

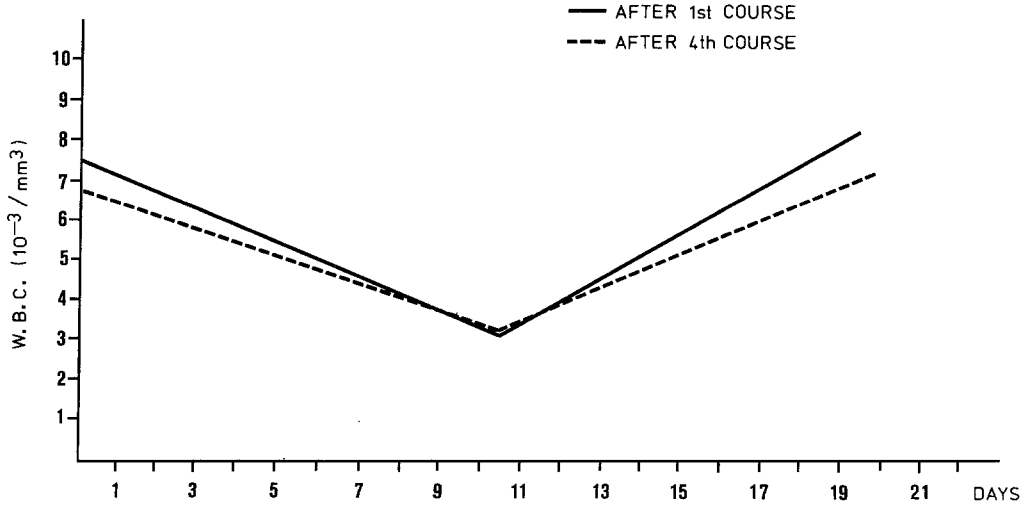

Fig. 1. Time course of the mean values of WBC counts after the first and fourth treatment course with 4′-epi-DX

The objective response was not evaluable in seven of 66 treated patients for the following reasons: withdrawal after the first treatment course because of rapidly progressive disease (5 patients), protocol deviation (1 patient) and inadequate follow-up (1 patient). Out of 59 evaluable patients, nine (15%) had PR, five (9%) had MR, 25 (42%) had NC, and 20 (43%) presented P. The median duration of PR and MR was 6 months, respectively. An analysis of objective remission is reported in Table 4. Out of 17 cases of lung cancer, one case of epidermoid and one of large cell anaplastic achieved PR for 7 months and MR, respectively. Out of 13 heavily pretreated patients with metastatic breast cancer, four had PR lasting for 3–12 months and another two had MR. Another patient with advanced breast and concomitant primary gastric cancer had an objective remission > 50% in metastatic cutaneous lesions secondary to breast cancer and no change in gastric lesion. This patient was classified as having an MR of the total tumor lesions. Out of eight patients with head and neck cancer, one patient with pretreated recurrent tonsillar epidermoid carcinoma achieved a PR for 6 months. Of four patients with advanced gastric cancer, two had a PR for 4 and 5 months. A patient with advanced ovarian cancer previously irradiated and treated with chlorambucil achieved a PR. A patient with disseminated melanoma presented MR.

The median survival time was 9 months for PR and MR responders (range 3+ to 18+) and for patients showing NC (range 2 to 19+), whereas for patients with P the median survival time was 3 months.

Discussion

This study shows that 4′-epi-DX has a toxicity profile similar to that observed during DX treatment. The incidence and severity of acute side effects during treatment with 4′-epi-DX at IV single doses of 90 mg/m^2 are at the same level of those previously reported during treatment with the standard dose (60 mg/m^2) of DX [4] and lower than those observed in an our previous experience with DX at 80 mg/m^2 [10]. Considering that many of our patients were heavily pretreated with radiotherapy and/or chemotherapy, in our opinion these results confirm that 4′-epi-DX has a lower rate of acute toxicity, especially myelotoxicity, in comparison with its parent drug.

The relatively moderate acute toxicity of 4′-epi-DX compared with DX has already been reported [3, 7, 11]. It has been suggested [9] that this effect may be the biological consequence of the pharmacokinetic characteristics of the compound, which gives rise to plasma levels constantly lower

Table 3. Monitoring of cardiac function during 4′-epi-DX treatment (mean values ± ES)

	No. patients	Basal	After 90 mg/m^2	After 360 mg/m^2	After 540 mg/m^2
QRS height (mm)[a]	16	4.99 ± 0.445	4.78 ± 0.419	4.52 ± 0.339	4.40 ± 0.333[b]
EF (%)	9	61.66 ± 2.915	60.40 ± 2.50	66.66 ± 1.997	–
PEP/LVET	6	0.318 ± 0.039	0.315 ± 0.034	0.335 ± 0.037	–

[a] According to Minow et al. [8]
[b] $P < 0.02$

Table 4. Analysis of objective remission

	No. evaluable patients	No. pretreated patients	PR	MR
Lung	17	8	1	1
Epidermoid	6	4	1	–
Adenocarcinoma	3	1	–	–
Large cell	2	–	–	1
Small cell	2	1	–	–
Not specified	4	2	–	–
Breast	13	12	4	2
Head and neck	8	6	1	–
Stomach	4	2	2	–
Melanoma	3	2	–	1
Ovary	1	1	1	–
Breast and stomach	1	1	–	1
Sarcoma	2	1	–	–
Kidney	2	1	–	–
Endometrium	2	2	–	–
Others[b]	6	2	–	–
Total	59	38	9 (15%)	5 (9%)

[a] Radiotherapy and/or chemotherapy
[b] Bladder, lymphoma, rectum, lung + rectum, testis, primary site unknown

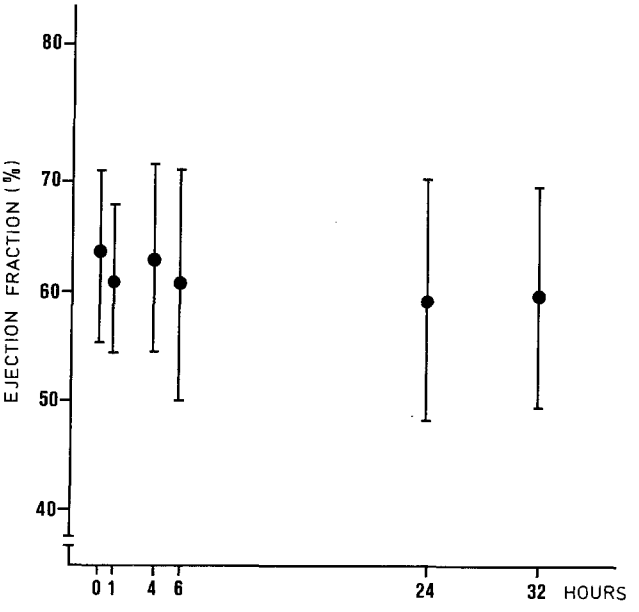

Fig. 2. Monitoring of the ejection fraction (EF) by angiocardiography in nine patients after 90 mg/m^2 of 4′-epi-DX (means ± SD)

than those observed after the administration of an equal dose of DX.

No definite conclusion is possible about the cardiotoxicity of 4′-epi-DX. During the treatment one patient presented a transient tachycardia, and minor occasional ECG changes were recorded in some other patients. As previously reported with DX [8], we detected a decrease in the height of QRS voltage on the ECG after a cumulative dose of 540 mg/m^2 of 4′-epi-DX, but no case of congestive heart failure was found. These results suggest that further careful investigations on the cardiotoxic effects of the drug might be carried out also with cumulative doses higher than those used in the present study.

As far as the therapeutic activity of 4′-epi-DX is concerned, a PR was achieved in 15% of 59 evaluable patients and MR was obtained in another 9%. PR was seen in cases with DX-sensitive tumors like breast, lung, gastric, and ovarian cancer. Out of 13 heavily pretreated patients with advanced breast cancer, 4′-epi-DX induced PR in 31%. If confirmed in a greater number of patients, this result could indicate that 4′-epi-DX is as active as DX in advanced breast cancer. Out of 17 patients with lung cancer 4′-epi-DX showed PR only in one case with epidermoid carcinoma. Oriented phase II trials might clarify the activity of the drug in non-small cell lung cancer.

In conclusion, this trial suggests that a broader study of 4′-epi-DX in mono and polichemotherapy regimens is justified in patients with DX-sensitive tumors in order to verify that this new DX derivative possibly has a better therapeutic index.

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