Phase I Trial of Esorubicin (4′Deoxydoxorubicin)

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A phase I study of 4′deoxydoxorubicin (esorubicin) was performed on an every-21-day bolus intravenous (IV) schedule in 36 patients with advanced cancer. Thirty-four patients were evaluable for toxicity analysis. Toxicity included mild nausea, occasional local skin reactions, and mild to moderate alopecia. Myelosuppression was dose limiting. Clinically evident congestive heart failure was not observed. However, two patients developed premature ventricular contractions. Overall, esorubicin was better tolerated than doxorubicin at equally potent doses. Although response analysis was not the primary objective of this phase I study, minor responses were observed in melanoma, breast cancer, lymphoma, and gastric cancer. On the basis of this study, a starting dose of 30 mg/m^2 IV every 21 days is recommended for good-risk patients with escalation to 32.5 mg/m^2 depending on bone marrow tolerance. For patients with poor bone marrow reserve, a starting dose of 25 mg/m^2 every 21 days is recommended. Phase II trials with esorubicin in this dosage schedule are clearly warranted in a wide variety of metastatic neoplasms including a substantial population of patients who have not received prior chemotherapy.

SINCE its introduction over a decade ago, the anthracycline antibiotic doxorubicin has proved to be one of the most effective anticancer agents currently in use. However, its prolonged use is limited by cardiac toxicity especially after the cumulative dose by bolus injection exceeds 500 to 550 mg/m^2. Consequently, new anthracycline analogs have been developed in an effort to decrease or eliminate cardiac toxicity while retaining anticancer activity. Structure-activity relationship studies have shown that the C-4′ position in the sugar moiety can be modified to provide analogs that may possess a more favorable therapeutic index than doxorubicin. 4′Deoxydoxorubicin (esorubicin) is a derivative of doxorubicin obtained by removal of the hydroxyl group from the 4′ position on the amino sugar (Fig 1). It was synthesized by Arcamone et al.[1] This chemical modification increases the basicity of the compound.

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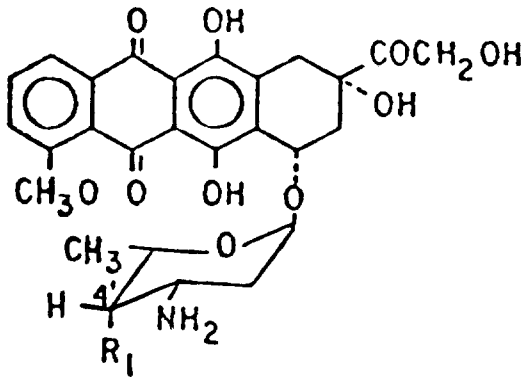
Esorubicin is at least as active as doxorubicin in several murine tumor models (L1210, P388, gross, and solid sarcoma 180).[1-5] It is slightly less active than doxorubicin in B16 melanoma and early and late mammary mouse carcinoma, but is more active in the colon 38 tumor.[2] It appears to be very active against several human colon tumor xenografts in nude mice.[2,6] In this system, its activity appears to be superior to both 5-fluorouracil and BCNU.[7] Overall, it appears to have greater antitumor potency than doxorubicin.

In vitro phase II studies of esorubicin, performed at the University of Arizona Cancer Center against a number of different human tumors using the human tumor stem cell assay, have also shown significantly increased antitumor potency of this drug against some tumors as compared to doxorubicin or daunorubicin.[8,9] However, significant in vitro antitumor activity was not observed against human colon cancer. In the stem cell assay, esorubicin appears to be noncross-resistant with doxorubicin.

In general, toxicology studies in animals have shown a pattern of toxicity that is similar to previously studied anthracycline drugs.[2] These include dose-dependent weight loss, myelosuppression, and gastrointestinal toxicity (vomiting, diarrhea and spontaneous hemorrhage). Liver and kidney toxicity was seen only at the highest doses used. Of great importance is the finding



doxorubicin R_1 = OH

4'deoxydoxorubicin R_1 = H

Fig 1. The structure of doxorubicin and esorubicin.

that, in comparison to doxorubicin, esorubicin markedly reduces or eliminates cardiac toxicity in all three animal models studied (ie, mouse, rabbit, and dog).[2,3] The LD10 in mice was 8.5 mg/kg and one tenth of this dose induced only mild toxicity in dogs.[2]

In November 1982, we initiated a phase I trial of esorubicin. Case accrual was completed in August 1983 after 36 patients had been entered on this study. Results of the phase I trial and a recommended dose schedule for phase II study are reported in this paper.

MATERIALS AND METHODS

Patient Selection

All patients entered into the study had histologic proof of cancer and were refractory to conventional methods of treatment. All patients had an estimated life expectancy of at least eight weeks, a Karnofsky performance status of ≥50, and had recovered from the effects of previous chemotherapy or radiotherapy. Patients were required to have adequate liver function (total bilirubin <2 mg/dL) and adequate renal function (serum creatinine <1.5 mg/dL or a creatinine clearance >80 mL/min). Adequate bone marrow function was required, ie, a peripheral absolute granulocyte count >1,500/μL and a platelet count >100,000/μL. Patients with a previous history of congestive heart failure or serious arrhythmia as well as those with prior total dose of doxorubicin >350 mg/m² were excluded. One exception to this was a patient with a total doxorubicin dose of 363 mg/m² who had a normal nuclear medicine cardiac ejection fraction of 62%. Patients who had received between 300 to 350 mg/m² of doxorubicin were evaluated with a nuclear medicine cardiac ejection fraction that was required to be normal prior to initiation of the drug.

Parameters Evaluated During Study

Pretreatment evaluation consisted of a history and physical examination, complete blood cell (CBC) count, electrolytes, blood sugar, calcium, phosphorus, uric acid, liver function tests, thyroxine, amylase, prothrombin time, partial thromboplastin time, and urinalysis. An initial chest roentgenogram and other radiographs as needed were obtained. A baseline electrocardiogram was obtained on all patients. During the study, weekly vital signs and CBC counts were measured. Prior to each course, CBC counts, serum chemistries, chest roentgenogram or other appropriate roentgenograms, and electrocardiogram were performed. During the first course of treatment, an electrocardiogram was obtained at one hour, 24 hours, and one week after drug administration. In subsequent courses, an electrocardiogram was obtained one hour after each drug infusion. Nuclear medicine ejection fractions were measured after every eight courses of treatment in patients with <200 mg/m² of prior doxorubicin and five courses in patients who had previously received 200 to 350 mg/m² of doxorubicin. If a nuclear medicine injection fraction became abnormal, an endomyocardial biopsy was planned; however, this was not required in any patient.

Toxicity Criteria

Toxicity criteria were essentially those of the Southwest Oncology Group. Those criteria pertinent to this study are summarized in Table 1. Alopecia was graded as mild (<25% hair loss), moderate (25% to 75%), or severe (>75%).

Although primarily a phase I study, patients were observed for response according to the following criteria: complete response, total disappearance of all clinical evidence of disease for at least two measurements separated by at least four weeks; partial response, at least a 50% reduction in the size of all measurable tumor areas as measured by the sum of the products of the greatest length and the maximum width; and minor response, a decrease in size of measurable tumor areas, but less than that required for a partial response. Patients who failed to show any reduction in tumor size or showed tumor progression were considered nonresponders.

Drug Information and Schedule

Esorubicin (NSC #267469; IMI-58; 4'deoxydoxorubicin) was supplied in 5-mg vials as a red powder by Farmitalia Carlo Erba, Milan, Italy. It was reconstituted in 5 mL of 5% dextrose in water for injection. The drug was given by intravenous (IV) injection over five minutes every three weeks. The lowest starting dose for the phase I trial was 10 mg/m.[2] Patients without evidence of myelosuppression or other toxicity at three weeks after drug administration were eligible to reenter the study at the same dose or at a higher dose level. Patients were classified as "new patients" only for the initial dosage level and not on reentry. If severe toxicity was encountered, dose reduction was permitted at the next treatment cycle. Treatment was discontinued if disease progression became clearly evident.

RESULTS

Patient Characteristics

The total number of patients entered was 36; their characteristics are shown in Table 2. Two

Table 1. Summary of Relevant Toxicity Criteria

Toxicity	Grade 0	1	2	3	4
Hematologic					
Granulocytes/μL	>1,500	<1,500	<1,000	<500	<250
Platelets/μL	≥100,000	75,000–99,999	50,000–74,999	25,000–49,999	<25,000
Gastrointestinal					
Stomatitis	Normal	Erythema	Ulcers, able to eat	Unable to eat because of ulcerations	
Nausea and vomiting	None	Nausea, no vomiting	Vomiting can be prevented by therapy (<6 times/d)	Vomiting >6 times/d in spite of antiemetics	

patients were inevaluable for toxicity analysis since they failed to obtain follow-up evaluation after the first course. Five patients are currently inevaluable for response. These include the two mentioned above as well as three others who refused to continue treatment after the first course.

The median number of courses of esorubicin per patient was 2.5 (range, 1 to 11). Five patients were given one course, 13 received two, seven received three, seven received four, two received six, one received ten, and one received 11 courses of treatment. The median total dose per patient was 62.5 mg/m^2 (range, 25 to 222 mg/m^2). Table 3 lists the doses and courses administered during this study. Patients entered at 17.5 and 22.5 mg/m^2 received these doses after experiencing toxicity at higher doses. These were, therefore, not part of the planned dose escalation. The 27.5 mg/m^2 dose was also not part of the planned dose escalation schedule, with patients being entered at this dose either because of toxicity at a higher dose or because they were considered to have poor bone marrow reserve by their primary physicians and, thus, given a lower starting dose than 30 mg/m^2.

Toxicity

Table 4 lists the toxicity encountered after a single dose of the drug. Only grade 1 nausea (ie, nausea, but no vomiting) was observed. One patient developed grade 1 stomatitis at her entry dose of 35 mg/m^2 as well as at a reduced dose of 27.5 mg/m^2. This was transient, lasting only two to four days each time. Local reactions consisted of hives at the injection site, occasionally extending proximally along the venous track. Once encountered, these reactions tended to recur in the same patients. In one patient, recurrent local reactions led to a decrease in the administered dose. Since local reactions tended to recur in patients, subsequent doses in the same patient

Table 2. Patient Characteristics

Characteristic	No.
Total no. of case entries	36
No. evaluable for toxicity	34
No. evaluable for response	31
Sex	
Male	13
Female	23
Age in yr (range)	21–73
Median Karnofsky performance status (range)	80 (50–100)
No. with prior chemotherapy	33
Median no. of prior chemotherapy regimens (range)	2 (0–5)
Prior doxorubicin	20
Prior radiotherapy	19

Table 3. Doses and Courses of Esorubicin

Dose (mg/m^2)	No. of Patients Evaluable/ No. Entered	Total No. of Courses Evaluable/Total No. Courses
10	4/4	6/6
15	7/7	13/14
17.5	3/3	3/3
20	6/7	20/21
22.5	2/2	2/3
25	10/10	19/19
27.5	3/4	3/4
30	16/16	24/24
32.5	9/10	13/16
35	1/1	1/1
Total	61/64 (95.3%)	104/111 (94%)

Table 4. Toxicity After a Single Dose of Esorubicin

Dose Level (mg/m^2)	Nausea	Local Reactions	Alopecia	Granulocytopenia	Thrombocytopenia	Cardiac
10	1/6	2/6	0/6	0/6	0/6	0/6
15	3/13	1/13	0/13	2/13 (both grade 2)	0/13	0/13
17.5*	0/3	1/3	0/3	1/3 (grade 2)	0/3	0/3
20	1/20	3/20	0/20	3/20 (2 grade 1, 1 grade 2)	7/20 (6 grade 1, 1 grade 3)	1/20 (PVCs)
22.5*	2/2	0/2	1/2 (mild)	1/2 (grade 2)	0/2	0/2
25	3/19	0/19	3/19 (2 mild, 1 moderate)	10/19 (7 grade 1, 2 grade 2, 1 grade 3)	1/19 (grade 1)	1/19 (PVCs, trigeminy)
27.5*	0/3	1/3	0/3	3/3 (1 grade 3, 2 grade 4)	3/3 (2 grade 3, 1 grade 4)	0/3
30	9/24	2/24	4/24 (2 mild, 2 moderate)	14/24 (2 grade 1, 3 grade 2, 5 grade 3, 4 grade 4)	5/24 (2 grade 1, 2 grade 3, 1 grade 4)	0/24
32.5	2/13	1/13	3/13 (2 mild, 1 moderate)	11/13 (3 grade 1, 5 grade 2, 3 grade 3)	2/13 (1 grade 2, 1 grade 3)	0/13
35	0/1	0/1	1/1 (moderate)	1/1 (grade 4)	1/1 (grade 2)	0/1

NOTE. The data in this table show the No. of courses in which the indicated toxicity was encountered/total No. of courses at that dose. PVC = premature ventricular beats.

*These doses were not part of the planned dose escalation (see text).

were always preceded with premedication. Consequently, Table 4 probably underestimates the total frequency of local reactions that would have been encountered in the absence of premedication with diphenhydramine and/or steroids, which usually prevented or reduced the intensity of the reactions. Regional skin cooling may also block local reactions. Overall, 22% (8/36) of the patients experienced local reactions.

Myelosuppression was the dose-limiting toxicity. Granulocyte and platelet nadirs usually occurred at the two-week measurement, but could be seen as early as one week after drug administration. Recovery usually followed within four to seven days after the nadir. Two patients developed fevers during the granulocytopenic period and received broad-spectrum antibiotic treatment. One of these two was a previously untreated patient with adenocarcinoma of unknown origin with metastases to the liver who received the highest dose tested in this study (35 mg/m^2). Table 5 shows the hematologic toxicity after the first course of esorubicin in new patient entries at the planned dose levels.

Congestive heart failure was not encountered in any patient. One patient with metastatic colon cancer and massive ascites developed premature ventricular beats and occasional trigeminal rhythm within 24 hours after receiving one course of treatment. A second patient developed premature ventricular beats after receiving 222 mg/m^2 of esorubicin over ten courses. He had previously been treated with doxorubicin-containing regimens to a total doxorubicin dose of 240 mg/m^2. Three patients fulfilled the planned criteria for measurement of cardiac ejection fraction. They had received 90 mg/m^2, 240 mg/m^2, and 250 mg/m^2 of doxorubicin prior to entry and

Table 5. First-Course Hematologic Toxicity of Esorubicin in New Patients

Dose (mg/m^2)	No. of New Patients Evaluable (No. Escalated)	Nadir Counts After First Course*	
		Granulocytes	Platelets
10	3 (2)	6.2 (4.8–19.6)	370 (326–374)
15	3 (0)	1.6 (0.6–4.7)	246 (141–396)
20	2 (0)	1.35 (1.1–1.6)	176 (175–177)
25	4 (0)	2.1 (0.8–2.7)	323 (197–458)
30	13 (1)	0.61 (<0.25–4.2)	134 (3–665)
32.5	6 (0)	0.85 (<0.25–1.8)	230 (44–282)
35	1 (0)	<0.025	74

* $\times 10^3/\mu L$.

had normal follow-up ejection fractions (58%, 61%, and 65%). One patient had an acute myocardial infarction two weeks after his fourth course at the 30 mg/m^2 dose level. However, this was not considered to be related to the drug. He recovered uneventfully and subsequently received additional chemotherapy with other agents.

Therapeutic Activity

Although not the primary objective of this study, patients were monitored for tumor response. No complete or partial responses were observed. However, clearly documented minor responses were seen in 29% (9/31) of the evaluable patients. Eight of these nine responding patients had received prior doxorubicin. Table 6 summarizes the tumor types of patients studied and response information on patients who were evaluable for response. Table 7 lists previous treatment received by the responding patients and the dose of esorubicin at which the minor response occurred.

Table 6. Therapeutic Activity of Esorubicin (Phase I Trial)

Tumor Type	No. Evaluable Patients	Response
Hypernephroma	1	...
Sarcoma	3	...
Melanoma	4	1 (minor)
Colon	5	...
Breast	5	2 (minor)
Lymphoma (non-Hodgkin's)	3	2 (minor)
Lymphoma (Hodgkin's)	4	3 (minor)
Gastric	2	1 (minor)
Carcinoid (thymic)	1	...
Lung (non-small cell)	1	...
Mesothelioma	1	...
Unknown primary	1	...
Total	31	9 minor (29%)

DISCUSSION

On the basis of this phase I trial, the dose-limiting toxicity of esorubicin appears to be myelotoxicity. Since CBC counts were only measured at weekly intervals, the exact day of hematologic nadir could not be precisely estimated. The nadirs usually occurred at the 14-day measurement, but occasionally were seen seven days after a dose. Thus, the nadir occurred between one to 14 days for the majority of patients.

It appears that esorubicin is about twice as potent as doxorubicin with respect to myelosuppression. For phase II trials, we would recommend a starting dose of 30 mg/m^2 given every 21 days for good-risk patients. If this dose is tolerated without myelosuppression, escalation to 32.5 mg/m^2 should be considered. For previously untreated patients, higher doses may prove tolerable. For patients with poor bone marrow reserve (ie, heavily pretreated with chemotherapy and/or radiation therapy), we would recommend a starting dose of 25 mg/m^2.

There is too little clinical information at present on cardiac toxicity, but preclinical data suggest that this will be significantly less than that seen with doxorubicin. More information on this issue will be obtained in phase II trials wherein

Table 7. Characteristics of Responding Patients

Diagnosis	No. Previous Chemotherapy Regimens	Dose of Esorubicin Producing Response (mg/m^2)
Melanoma	5	32.5
Breast	1	25
Breast	4	30
Non-Hodgkin's lymphoma	3	15
Non-Hodgkin's lymphoma	2	30
Hodgkin's disease	3	20
Hodgkin's disease	4	25
Hodgkin's disease	2	32.5
Gastric	1	27.5

NOTE. All patients except the one with melanoma had received prior doxorubicin. All responses were classified as minor responses.

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