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Early Cardiac Toxicity of 4′-Iodo-4′-deoxydoxorubicin

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4′-iodo-4′-deoxydoxorubicin was administered intravenously to 35 patients with advanced malignant neoplasms. The doses were escalated as follows: 2, 4, 6, 7, 10, 14, 19, 26, 52, 70, 80 and 90 mg/m². Myocardial function was assessed by Holter monitoring and echocardiography. The prevalence of arrhythmias that could be attributed to the drug in the 24 h following infusion was 14.3% (supraventricular) and 10.6% (ventricular). Echocardiographic heart function variables were unchanged at 24 h and 21 days from drug injection. The data indicate the absence of significant, acute cardiotoxic effects of 4′-iodo-4′-deoxydoxorubicin.
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INTRODUCTION

DELAYED CARDIOTOXICITY represents the major limitation to the use of anthracyclines in long-term treatment. Moreover, a transient decrease in myocardial contractility and cardiac arrhythmias, mainly represented by ventricular premature beats and repolarisation abnormalities, have been reported after anthracycline administration [1–3]. 4′-iodo-4′-deoxydoxorubicin (I-DOX) is an analogue of doxorubicin that is modified in the amino sugar, where the hydroxyl group at C4′ has been substituted with an iodine atom. The novel anthracycline has shown interesting antineoplastic activity. In fact, it was found more potent than doxorubicin on several murine and human tumour cell lines [4–8]. In preliminary tests performed in mice and rats, the analogue showed consistently less cardiotoxic activity than doxorubicin [7–9].

We report the results of an evaluation of cardiac function and cardiac electrical activity in a phase I trial which included 35 patients with metastatic carcinoma. The purpose of the trial was to determine, on the basis of a pharmacokinetically guided dose escalation, the maximum tolerated dose [10].

PATIENTS AND METHODS

The study was conducted on 35 patients suffering from different kinds of cancer: 10 gastrointestinal carcinomas, 5 kidney carcinomas, 5 non-small-cell lung carcinomas, 5 unknown primary carcinomas, 2 hepatocellular carcinomas, 2 breast cancers, 2 melanomas, 2 sarcomas, 1 ovarian carcinoma, and 1 non-Hodgkin lymphoma. 24 patients were men and 11 women; their median age was 47 years (range, 16–75). The patients were all in good general condition (median Karnofsky performance status, 90; range, 80–100). 4 patients had been previously treated with very low doses of anthracyclines (doxorubicin, median dose 180 mg/m²; range, 90–260) and 17 patients with other anticancer agents.

Patients with electrocardiogram (ECG) abnormalities of conduction and/or severe repolarisation alterations were excluded from the study. Moreover, patients with a previous history of heart disease or under treatment with diuretics, beta blockers, calcium antagonists, nitrates or vasodilators were also excluded from the study.

Evaluation of left ventricular contractility

Left ventricular M-mode echocardiogram, phonocardiogram, indirect carotid pulse tracing and blood pressure measurements were obtained simultaneously before and 24 h and 21 days after I-DOX injection. Peak systolic and diastolic blood pressure measurements were performed with a Dinamap 845 vital signs monitor (Critikon, Tampa, Florida). The percentage of fractional shortening of left ventricular minor axis (MAS%), the relative velocity of contraction (RVC), and the relation of left ventricular end-systolic wall stress (σ_{cs})/MAS% were used as indices of left ventricular contractility. RVC was calculated as previously described [11]. The relationship between left

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ventricular meridional wall stress at end-systole (σ_{es}) and MAS% was calculated as described elsewhere [12]. This parameter was adopted because it is load-independent and therefore particularly useful in the evaluation of the contractile state, especially in doxorubicin-treated patients [13, 14].

Holter monitoring

Holter recordings were done with a Dynacord model 419 instrument. All tapes were analysed using Del Mar Avionics model 500 equipment. The printed records of all ECG changes and arrhythmias were evaluated in a double blind trial by two of us. To maximise the yield, patients were encouraged, when possible, to be ambulatory and physically active and were instructed to maintain a diary of daily events and symptoms. Holter records were obtained in each patient the day prior to chemotherapy and the day of drug administration, starting 30 min before.

RESULTS

Sinus tachycardia (ST) (> 100 beats/min) was not recorded during or in the hours following drug administration. There were no episodes of significant ST segment elevation or depression exceeding 1 mm in any postinfusion recording. 2 patients had isolated supraventricular ectopy before treatment: one had normalisation of the ECG and the other had no change in the severity of the ectopy. 1 patient experienced supraventricular couplets, and another 1 supraventricular couplets plus an episode of supraventricular tachycardia of three beats in duration (both received a dose of 52 mg/m^2). Still another patient, with isolated supraventricular ectopic beats before treatment and who received a dose of 70 mg/m^2, had 30 episodes of supraventricular tachycardia of more than three beats in duration. Another patient treated with 80 mg/m^2 experienced five episodes of supraventricular tachycardia of more than three beats and an episode of atrioventricular dissociation with escape rhythm.

4 of 28 patients experienced isolated ventricular ectopy before I-DOX therapy. One of them had normalisation of the ECG, and in 2 patients the severity of the arrhythmias increased (all 3 received 70 mg/m^2). One of them experienced ventricular couplet and the second 1 some episodes of three consecutive ventricular premature beats. In contrast, the fourth patient, who had a normal ECG before treatment and who received 14 mg/m^2, had ventricular ectopy (ventricular couplets) after drug administration.

Tables 1 and 2, respectively, report the mean values of MAS% and RVC recorded before and 24 h and 21 days after treatment. No significant modifications of the parameters were observed in the range of doses tested.

The effect of different doses of I-DOX was also studied by determining the left ventricular σ_{es}/MAS% relation, which is considered a load-independent, highly sensitive index of left ventricular contractility [13, 14]. As shown in Fig. 1, at the higher doses of 52, 70 and 80 mg/m^2, no significant displacement of the curves was observed at 24 h or 21 days after drug administration.

Table 1. Percentage minor axis shortening (MAS%) observed before and at 24 h and 21 days after drug administration

Dose (mg/m^2)	No. of cases	Pretreatment	MAS% post-treatment	
			24 hours	21 days
2	3	37.1	37.2	–
		29.9	29.0	29.3
		31.9	32.3	27.5
4	4	40.0	39.1	36.5
		31.7	31.8	33.2
		27.0	26.9	26.8
		27.5	27.3	27.5
6.7	4	30.1	29.5	30.9
		35.2	33.5	37.3
		27.5	29.1	29.1
		30.4	29.6	35.6
10	3	25.9	26.7	26.6
		35.6	35.7	30.6
		33.9	34.7	34.4
14	3	40.4	38.5	38.8
		34.4	32.2	34.4
		36.6	35.6	35.5
19	3	34.5	33.3	36.7
		36.2	35.3	38.3
		35.5	36.7	35.1
26	3	36.7	34.3	37.1
		37.1	38.1	39.3
		30.9	29.1	29.6
52	4	36.0	29.7	31.0
		28.7	30.8	33.4
		35.8	36.0	35.4
		35.8	32.8	33.0
70	5	33.8 (1.4)*	33.0 (1.7)	35.2 (0.9)
80	7	34.6 (1.0)	34.2 (1.1)	33.8 (0.9)
90	2	33.4	32.5	–
		35.2	35.6	–

* Mean (S.E.).

DISCUSSION

Acute cardiac toxicity of anthracyclines occurs within hours of drug administration and includes transient left ventricular dysfunction [1, 2], pericarditis [15], and arrhythmias [3]. Sporadic observations of acute anthracycline-induced ECG alterations using standard 12-lead ECG recordings have reported electrical abnormalities in up to 41% of cases [3]. Such electrical abnormalities are considered non-specific and reversible. The introduction of continuous ambulatory monitoring and appropriate controls has made it possible to characterise the frequency and type of cardiac arrhythmia and depolarisation disturbance in the first hours of and 24 h following doxorubicin administration. ECG abnormalities, usually in the form of ventricular premature beats or unsustained ventricular tachycardia, occur more commonly from the second to the 24th hour, with an incidence of 24% [16, 17].

In our series of patients, only 4 (14.3%) experienced supraventricular arrhythmias ranging from couplets to an episode of supraventricular tachycardia, and 3 patients (10.6%) developed ventricular arrhythmias ranging from isolated ventricular beats to couplets or a brief run of unsustained ventricular tachycardia. 1 patient treated with 80 mg/m^2 had an atrioventricular dissociation with escape rhythm that was preceded by runs of tachycardia alternating with bradycardia. Since the rhythm disturbance occurred during an episode of vomiting, a direct implication of the drug in the aetiology of the abnormality can be excluded.

Table 2. Relative velocity of contraction (RVC) observed before treatment and at 24 h and 21 days after drug administration

Dose (mg/m²)	No. of cases	Pretreatment	RVC post-treatment 24 h	RVC post-treatment 21 days
2	3	1.05	1.12	–
		0.89	0.86	0.92
		0.95	1.12	0.82
4	4	0.98	1.04	0.82
		0.82	0.84	0.87
		0.75	0.79	0.68
		0.82	0.84	0.97
6.7	4	0.91	0.91	1.02
		1.02	0.82	1.12
		0.97	0.85	0.84
		0.77	0.83	0.95
10	3	0.84	0.84	0.89
		0.95	0.84	1.01
		0.91	1.06	1.04
14	3	1.18	1.16	1.07
		1.04	0.95	1.00
		1.11	1.08	1.06
19	3	1.06	1.04	1.05
		0.97	1.11	0.97
		1.06	1.08	1.13
26	3	1.08	1.00	0.89
		1.02	1.17	1.02
		0.85	0.86	0.83
52	4	1.10	0.91	0.91
		0.86	1.01	1.00
		0.86	0.92	0.92
		1.12	0.99	1.08
70	5	0.98 (0.07)	0.95 (0.08)	1.03 (0.02)
80	7	0.96 (0.05)	0.93 (0.05)	0.99 (0.02)
90	2	1.18	1.07	–
		1.05	1.16	–

Mean (S.E.).

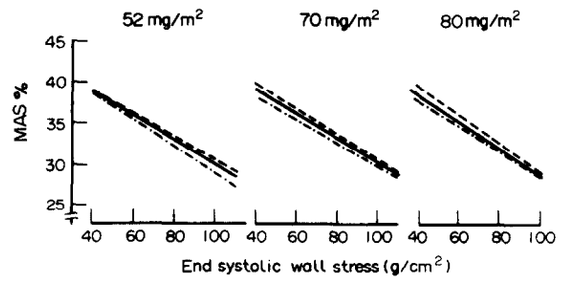

Fig. 1. Plot of the left ventricular end systolic wall stress (σ_{es})/percentage fractional shortening (%MAS) relation under resting conditions for patients treated wth 52, 70 and 80 mg/m² of iodo-doxorubicin. Curves represent the mean of pooled data points from several patients. —— Before treatment, – – – 1 day after treatment, – · – · 21 days after treatment.

Data from our patients demonstrated a relatively low incidence of arrhythmias after I-DOX administration, a tendency to increased severity of arrhythmias in cases with preexisting ECG abnormalities, and an occurrence mainly with the highest doses. The occurrence of arrhythmias in the hours following I-DOX administration could be attributed to the antineoplastic agent itself, although a non-specific response to enhanced sympathetic discharge surrounding the administration of phase I chemotherapy cannot be ruled out as a factor contributing to the arrhythmias.

The second aspect of acute anthracycline cardiotoxicity is represented by a transient left ventricular dysfunction [1, 2]. In our experience, I-DOX at the highest doses did not produce any modification of MAS% or RVC, or any displacement of the σ_{es}/MAS% relationship. Such results indicate that the new analogue is almost devoid of acute cardiac toxicity, at least up to the doses tested.

The present results are in contrast with those previously described for doxorubicin and epirubicin, for which a statistically significant difference was found between pretreatment values of contractile function parameters and those recorded 1 and 24 h after drug administration [1, 2, 18]. Since a relationship seems to exist between acute and delayed cardiac toxicity in experimental animals [19, 20] and probably also in humans, the possibility exists of a lower cardiotoxic activity of I-DOX than of doxorubicin in long-term treatment, as evidenced in experimental animals [9].

The pharmacological bases of the reduced acute cardiotoxicity remain to be ascertained. In particular, the effect of the drug on the more prominent action mechanisms ascribed to anthracyclines has not been investigated [9]. It cannot be excluded that the pharmacokinetic behavior of the new analogue could at least partially explain the reduced myocardial toxicity, as suggested by clinical and animal studies [9, 21].

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Phase II Study of Nimustine in Metastatic Soft Tissue Sarcoma

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The EORTC Soft Tissue and Bone Sarcoma Group has conducted a phase II trial in 33 eligible patients with metastatic soft tissue sarcoma with nimustine 100 mg/m^2 every 6 weeks. In 31 evaluable patients there were 3 (10%) partial responses lasting 4.5,6 and 7.5 months, and 5 cases of stable disease. 12 patients had progressive disease and 11 patients early progressive disease. Toxicity consisted mainly of leukopenia and thrombocytopenia and nausea and vomiting. It is concluded that nimustine has only minor activity in soft tissue sarcoma.
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INTRODUCTION

NIMUSTINE (ACNU) is a water-soluble nitrosurea [1]. Previous clinical studies with nimustine have mainly been performed in Japan. Responses have been observed in small cell lung cancer, non-small cell lung cancer, head and neck cancer, gastric cancer, uterine cancer, chronic myelocytic leukaemia, Hodgkin's and non-Hodgkin lymphoma and brain tumours [2, 3]. The experience with nimustine in sarcoma is very limited. In a collected series, two responses in 8 evaluable patients were reported [3]. Because of these interesting results and the great lack of effective drugs for soft tissue sarcomas a phase II study was initiated.

PATIENTS AND METHODS

Patients could enter the study if they fulfilled the following eligibility criteria: histologically proven advanced and/or metastatic soft tissue sarcoma, age 15–75 years, and performance status 0–2 (WHO). Patients were required to have measurable progressive disease. Recurrent tumour in irradiated areas was not permitted as the sole evaluable lesion, and pleural effusions or bony metastases were not considered to be measurable. Other criteria for exclusion were prior treatment with nitrosureas, chemotherapy in previous 4 weeks or previous treatment with more than four cytotoxic agents, a previous or concomitant different malignant tumour, serious concurrent disease, and central nervous system metastases. Prior to entry patients were required to have adequate hepatic excretory (serum bilirubin < 25 μmol/l) and kidney function (serum creatinine < 150 μmol/l) and bone marrow reserve (leucocytes $> 4 \times 10.9/l$, platelets $> 125 \times 10.9/l$).

Nimustine was given by slow intravenous injection at a dose of 100 mg/m^2 every 6 weeks. In pretreated patients the dose was

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