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Evaluation of Cardiac Toxicity of Idarubicin (4-Demethoxydaunorubicin)

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Abstract—*Cardiac toxicity of idarubicin (4-demethoxydaunorubicin), a new daunorubicin derivative, was tested in 49 phase II patients with advanced malignancies. In 26 patients the drug was given intravenously at a dose of 13 mg/m² and in 23 orally at a dose of 45 mg/m². Cardiac toxicity was evaluated by means of electrocardiography, left ventricular systolic time intervals, echocardiography and radionuclide cineangiography. The type and incidence of ECG abnormalities were comparable to those observed with other anthracycline analogs. Other functional parameters, serially measured to evaluate delayed cardiotoxicity in patients who received more than 65 mg/m² intravenously or 225 mg/m² orally, were not significantly different from pretreatment values. No patient developed clinical congestive heart failure. Only one patient exhibited a drop in the left ventricular ejection fraction of more than 15% from pretreatment values. These data indicate that idarubicin given orally or intravenously at the tested doses has no significant cardiotoxic activity in the range of the cumulative doses attained.*

INTRODUCTION

IDARUBICIN is a new daunorubicin derivative obtained by substitution of the C-4 methoxyl group in the D ring of the aglycone moiety with a hydrogen atom [1]. *In vivo* experiments have shown that the drug, when administered intravenously, is four to eight times more potent than daunorubicin against L1210, Gross leukemia and ascites sarcoma 180 [2, 3], and when administered orally in mice it is five to ten times more potent than daunorubicin and doxorubicin against ascitic L1210 and P388 leukemias [4]. Whereas daunorubicin was found to be active orally only at extremely high doses [5], idarubicin administered orally in tumor-bearing mice (such as Gross leukemia and sarcoma) was active at a dose only four times higher than the optimal intravenous dose [6].

Acute and delayed toxicities following idarubicin administration were similar to those observed with parent compounds, but cardiac toxicity in rabbits and mice was comparatively lower. In particular, cardiac damage was observed only in animals treated with intravenous doses which resulted in late mortality, whereas daunorubicin induced myocardial lesions after administration of nonlethal doses [3, 5, 7].

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We report the results of cardiac function evaluation in a phase II trial which tested idarubicin in 49 patients with different neoplastic diseases treated at the Istituto Nazionale Tumori of Milan.

PATIENTS AND METHODS

A phase II trial to test idarubicin was carried out on 49 patients of both sexes (40 females and nine males) who were affected by different neoplastic diseases. In 26 patients (19 females and seven males; median age, 47.9 years; range, 10–65) the drug was given intravenously at a dose of 13 mg/m², and in 23 patients (21 females and two males; median age, 47.9 years; range, 17–64) the drug was administered orally at a dose of 45 mg/m². The treatment was repeated at intervals of at least 3 weeks. Idarubicin was kindly supplied by Farmitalia-Carlo Erba (Milan, Italy).

Among patients who received the drug intravenously, six had been previously treated with doxorubicin (cumulative doses, 75, 137, 240, 262, 400 and 540 mg/m²), three suffered from mild hypertension, and three had previously received radiotherapy (40 Gy rad to the mediastinum, 56 Gy rad to the left lung, and 32 Gy rad to the cervical column, respectively). Among the 23 patient who received idarubicin orally, three had been previously treated with doxorubicin (cumulative doses 120, 250 and 525 mg/m²), one had previously received radiotherapy (36 Gy rad to the mediastinum), and one

suffered from mild hypertension. No patient had received chemotherapy or radiotherapy during the 3 weeks preceding the beginning of drug administration. Patients with a previous history of congestive heart failure or arrhythmias were excluded from the study.

Cardiologic evalution consisted of systemic recording of arterial blood pressure, heart rate, electrocardiogram (ECG), left ventricular systolic time intervals (PEP/LVET ratio), echocardiography and radionuclide left ventricular ejection fraction (LVEF). For the study of acute cardiotoxicity, ECGs were recorded 30 min before each drug administration. This evaluation was repeated 1–3 h and 24 h after drug administration. Systolic time intervals were recorded while patients were fasting and at rest for at least 20–30 min before drug injection and 1 h, 1 day and 21 days after drug administration in patients treated intravenously, and 1 h, 3 h, 1 day and 21 days after drug administration in patients treated orally. In patients who received multiple doses, evaluation of cumulative cardiac toxicity was planned every three courses using systolic time intervals (PEP/LVET ratio), echocardiography and the radionuclide LVEF. Systolic time intervals were determined according to the methods described by Weissler *et al.* [8].

M-mode echocardiography was performed with an Ekoline 21 Smith-Kline instrument. The percentage of fractional shortening of the left ventricular minor axis and the relative velocity of contraction were used as indices of left ventricular contractility. Percentage minor axis shortening (MAS%) was defined as LVIDd − LVIDs/LVIDd × 100, where LVIDd is the left ventricular diameter in the end diastole and LVIDs is the left ventricular diameter in the end systole. The relative velocity of contraction (RVC) was defined according to Knapp [9] as VCF/0.14 + 0.014 × HR, where VCF is the mean velocity of circumferential fiber shortening and HR is the heart rate.

LVEF was assessed by means of radionuclide angiocardiography. Equilibrium-gated radionuclide angiocardiography was performed at rest in the supine position and in the left anterior oblique projection, following labeling of erythrocytes with ^{99}Tc by an *in vivo* technique [10]. The blood pool of patients was imaged by a small-field gamma camera (Selo model KR7) equipped with a general purpose parallel hole collimator. The gamma camera and an ECG gate (model Life Trace 12, Albury Instruments) were interfaced to a Digital PDP11 computer. Rest left ventricular ejection fraction was analyzed with commercially available software (Gamma 11) and was considered normal when greater than 50%.

RESULTS

Among the 26 patients treated intravenously, two received a cumulative dose of less than 26 mg/m^2, 11 beween 26 and 65 mg/m^2, and 13 more than 65 mg/m^2 (mean, 92.9 mg/m^2). The highest total dose administered was 169 mg/m^2. Among the 23 patients treated orally, four received a cumulative dose of less than 100 mg/m^2, nine between 100 and 225 mg/m^2, and 10 more than 225 mg/m^2 (mean, 288 mg/m^2). The highest dose administered orally was 495 mg/m^2.

Acute cardiac toxicity was detected by recording ECG changes and systolic time intervals. ECG abnormalities (Table 1) observed after idarubicin administration were mainly represented by tachycardia and arrhythmia; some patients developed ST-T segment changes. The incidence of ECG abnormalities was higher in patients treated intravenously than in those treated orally. The incidence appears to be independent of previous chemotherapy with anthracyclines; the difference between patients treated intravenously and those treated orally was not statistically significant. Nineteen patients were evaluated for acute cardiotoxicity by means of systolic time intervals: 10 received the

Table 1. *ECG changes observed in* 49 *patients on idarubicin treatment* (*ECGs were recorded* 30 *mins before*, 1–3 *and* 24 h *after each drug administration*)

	Idarubicin orally (n = 23)		Idarubicin i.v. (n = 26)	
	No. of cases	%	No. of cases	%
Sinus tachycardia	1	4.3	4	17.3
Sinus bradycardia	1	4.3	—	—
Arrhythmia				
Atrial premature beats	2	8.6	3	11.5
Ventricular premature beats	—	—	1	3.8
ST-T changes				
Flattening of the T wave	1	4.3	1	3.8
Inversion of the T wave	1	4.3	1	3.8
No. with 1 ECG alteration only	4	17.3	6	23.0
No. with 2 ECG alterations	1	4.3	2	7.6
Total	5	21.7	8	30.6

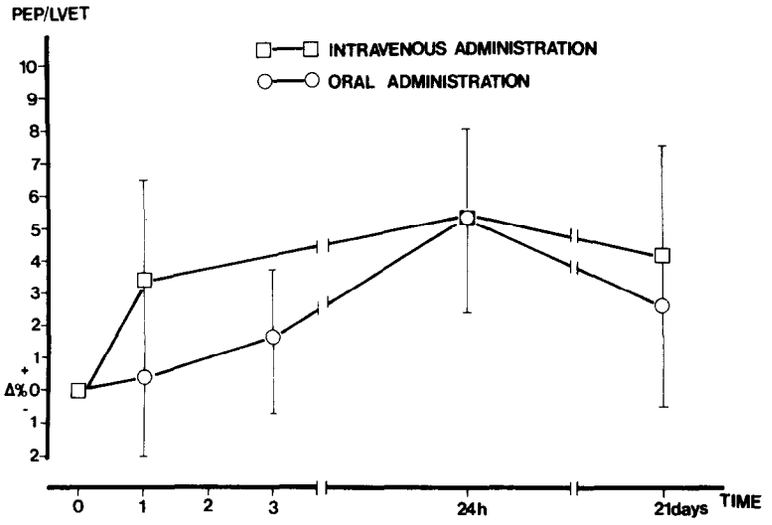

Fig. 1. Time course of the PEP/LVET ratio after administration of idarubicin, intravenously (□) *at* 13 mg/m², *and orally* (○) *at* 45 mg/m² (*mean* ± *S.E.*).

drug intravenously and nine orally. As shown in Fig. 1, the drug produced an increased in the PEP/LVET ratio, which reached the maximum 24 h after drug administration and partially regressed after 21 days. The differences from basal values were not statistically significant.

As shown in Table 2, in patients who received intravenously a cumulative dose of idarubicin of more than 65 mg/m², mean values of myocardial function parameters (PEP/LVET, MAS%, RVC, LVEF) failed to show statistically significant differences from mean basal values. Similarly, even in patients given idarubicin orally who received more than 225 mg/m², mean values of myocardial function parameters did not change in comparison to pretreatment values. Only a few patients developed a fall in myocardial function parameters of more than 15% of the pretreatment values (see Table 3). In particular, it should be stressed that only one patient who received intravenously a cumulative dose of more than 65 mg/m² had a fall in LVEF of more than 15%. The patient had no risk factors such as previous doxorubicin therapy, previous radiotherapy or hypertension. No such fall was observed in any patient who received idarubicin orally.

DISCUSSION

Anthracycline analogs are known to produce in humans early cardiotoxic effects represented by transient left ventricular dysfunction [11, 12] and non-specific ECG alterations [13], whereas a delayed effect of cumulative doses is represented by a specific cardiomyopathy [13]. In patients treated with the new analog idarubicin, ECG alterations were mainly represented by tachycardia, ectopic premature beats and modifications in the ST-T segment. It can be therefore concluded that the type of changes did not differ from that observed in patients treated with other anthracyclines such as doxorubicin, 4′-epi-doxorubicin and 4′-deoxy-doxorubicin, monitored with the same frequency [14, 15]. Moreover, the incidence was comparable to that observed with the aforementioned drugs. No significant difference was found in relation to the route of administration, thus confirming that the two routes of administration have the same biological effect, particularly in relation to the toxic effect on the heart.

Evaluation of the PEP/LVET ratio showed that the two treatments, oral and intravenous, produced the same increase in this parameter 24 h after drug administration, which partially persisted after 21 days after drug administration. However, the differences from pretreatment values were not statistically significant. This observation is in contrast to that previously described for doxorubicin and 4′-epi-doxorubicin [12, 14], for which a statistically significant difference was found. This observation suggests a non-significant acute cardiotoxic activity of this new analog, at least at the tested doses.

As regards cumulative cardiac toxicity recorded in patients who received more than 225 mg/m² orally or more than 65 mg/m² intravenously, myocardial function parameters did not show any significant difference from mean basal values. Very few patients showed a fall in echocardiographic ventricular function parameters (4/33 = 12.1% for MAS% and 5/33 = 15% for RVC). Two of these had risk factors such as previous doxorubicin therapy in one patient and previous radiotherapy in the other. Only one of the 27 patients (3.7%) evaluated with isotope angiocardiography had a fall in LVEF, which is considered the most sensitive and predic-

Table 2. Left ventricular function in patients who received idarubicin, more than 65 mg/m² *i.v. or more than* 225 mg/m² *orally (mean ± S.E.)*

	Intravenous administration				Oral administration			
	No. of cases	Before treatment	After treatment	*P*	No. of cases	Before treatment	After treatment	*P*
Heart rate	13	74.3 ± 4.3	75.2 ± 6.2	NS	10	74.0 ± 3	79.0 ± 3	NS
Blood pressure	13	126/80	125/78	NS	10	128/77	125/78	NS
PEP/LVET	11	0.344 ± 0.020	0.357 ± 0.030	NS	8	0.311 ± 0.020	0.330 ± 0.010	NS
Minor axis shortening (%)	11	31.4 ± 1.1	30.4 ± 0.8	NS	8	31.8 ± 1.8	31.6 ± 2.3	NS
Relative velocity of contraction	11	0.85 ± 0.06	0.82 ± 0.03	NS	8	0.88 ± 0.06	0.83 ± 0.07	NS
Left ventricular ejection fraction	9	67.5 ± 1.6	63.4 ± 1.1	NS	9	65.6 ± 2.5	64.7 ± 3.2	NS

Table 3. Percentage of patients with a drop in minor axis shortening %, relative velocity of contraction, and left ventricular ejection fraction of more than 15% *in comparison to pretreatment values*

	Intravenous cumulative dose (mg/m²)						Oral cumulative dose (mg/m²)					
	26–64 No./tot	%	≥65 No./tot	%	Total No./tot	%	100–224 No./tot	%	≥225 No./tot	%	Total No./tot	%
Minor axis shortening %	0/5	—	1/11	9.0	1/16	6.2	2/9	22	1/8	12.5	3/17	17.6
Relative velocity of contraction	0/5	—	2/11	18.1	2/16	18.4	2/9	22	1/8	12.5	3/17	17.6
Left ventricular ejection fraction	0/4	—	1/9	11.1	1/13	7.6	0/5	—	0/9	—	0/14	—

tive test among the noninvasive ones [16]. It should be stressed that echocardiographic signs of cardiac function impairment were observed only in one of the nine patients who had been previously treated with doxorubicin. The cumulative dose of doxorubicin was 120 mg/m^2, whereas that of idarubicin by oral route was 180 mg/m^2. No patient developed clinical congestive heart failure, and the changes in LVEF were minimal throughout the treatment, in agreement with the results of Bastholt and Dalmark [17]. These data therefore suggest that this new analog has no significant cardiotoxic effects, at least in the range of the tested doses.

As regards the problem of the comparative cardiotoxic potential of the two routes of administration, a higher incidence of cardiotoxic effects could be expected in patients treated by the intravenous route in the light of the knowledge that the peak plasma concentration of anthracyclines is highly correlated to the cardiotoxicity of these drugs. Owing to the limited number of patients and the cumulative doses they received, a definitive conclusion cannot be drawn. Similarly, no definitive statements can be made about the possible lower cardiotoxicity of idarubicin in comparison to parent compounds, although it has been recently reported that idarubicin in the rat model has significantly lower cardiotoxicity than doxorubicin [18].

The pharmacologic basis of this supposed reduced cardiotoxic activity remains to be clarified. In fact, no specific studies have been undertaken to ascertain the effect of the drug on the biological events influenced by anthracylines, which have potentially toxic consequences for heart cells such as (a) blockade of DNA, RNA and protein synthesis and fragmentation of DNA, (b) inhibition of binding to the membrane, with consequent alteration in membrane function, and finally (c) the formation of oxygen free radicals [19].

In conclusion, present data suggest that idarubicin given orally or intravenously at the tested schedules has no significant cardiotoxic effects in the range of the cumulative doses attained.

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