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PHASE I STUDY OF 4-DEMETHOXYDAUNORUBICIN BY ORAL ROUTE IN PATIENTS WITH ADVANCED CANCER

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Abstract

In a phase I trial 4-demethoxydaunorubicin (4-dm DNR) was administered as oral capsules once a week to 51 adults with advanced mainly gastrointestinal solid tumors. No fatal toxicity was observed at doses up to 25.0 mg/m^2. Dose-limiting granulocytopenia and non-hematologic toxicity developed at dosages $\geq$22.5 mg/m^2. No response to the therapy was observed. The plasma concentrations of 4-dm DNR were measured in 4 of the patients.

Key words: Chemotherapy; 4-demethoxydaunorubicin, phase I study, plasma concentrations.

In 4-demethoxydaunorubicin (4-dm DNR), a new anthracycline analogue of daunorubicin, the C-4 methoxyl group in the D ring of the aglycone moiety is substituted for a hydrogen group. After intravenous administration 4-dm DNR has demonstrated activity against L1210, Gross leukemia, and ascites sarcoma 180 at doses 4 to 8 times lower than the effective doses of the parent analogue, daunorubicin (1, 3). In a phase II trial, patients with advanced breast cancer, receiving 4-dm DNR 45 mg/m^2 orally every third week, revealed a response rate and a toxicity pattern comparable to those for patients registrated following treatment with doxorubicin (2). The present phase I study was performed in order to determine the maximum tolerable dose (MTD) of 4-dm DNR weekly administered by oral route, to describe the toxicity of 4-dm DNR, and to study its possible therapeutic activity in patients with advanced cancer (5).

Material and Methods

Patient selection. A total of 51 patients between 18 and 75 years of age with a histologically confirmed diagnosis of a malignant solid tumor refractory to conventional therapy were eligible. General characteristics of the patient material are shown in Table 1. Informed consent was obtained in all cases. Criteria for entry included: performance status (WHO criteria) $\leq$2, recovery from the toxic effects of prior chemotherapy or radiotherapy, leucocytes $\geq 4\times10^9$/l, blood platelets $\geq 100\times10^9$/l and hemoglobin $\geq$7 mmol/l, plasma-creatinine $\leq$0.120 mmol/l, normal Chrome-EDTA-clearance, plasma-bilirubin $\leq$21 μmol/l, plasma-coagulation factors $\geq$50%, plasma-albumin $\geq$0.5 mmol/l, plasma-alkaline phosphatases $\leq$344 units/l, plasma-aspartate-aminotransferase $\leq$50 units/l, and normal electrocardiograpy (ECG) and radionuclide angiocardiography (MUGA).

4-dm DNR was supplied as 5 mg, 10 mg and 25 mg gelatine capsules for oral use by Farmitalia Carlo Erba, Milan, Italy.

The first patients were treated with 2.5 mg/m^2 4-dm DNR weekly. The dose level was increased in steps of 2.5 mg/m^2. Each dosage level included at least 3 patients, and each patient was continuously treated with a fixed dose of 4-dm DNR. Approaching the MTD, the number of patients in each dose level was raised to a minimum of 6. A light meal was served just before the patient swallowed the gelatine capsules. The patients were seen weekly in our out-patient clinic. Pertinent history, physical examination, hematology and other blood samples, and urine analysis were repeated on each visit. The following types of non-hematologic toxicity were registrated weekly: allergy, alopecia, diarrhea, decreased performance status, fever, hematuria, hemorrhage, infection, influence on state of consciousness, pain, and peripheral neurotoxicity. Also toxic reactions in oral cavity, lungs or skin were

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registrated weekly. The ECG and MUGA examinations were recorded at 6-week intervals. Other studies were repeated when clinically indicated.

The treatment was stopped when progressive disease or unacceptable toxicity occurred, when a cumulated dose of 320 mg 4-dm DNR/m^2 was reached, or if the patient wanted to interrupt treatment.

The WHO criteria (9) for toxicity and response were employed. Toxicity exceeding 2 according to the WHO criteria was defined as unacceptable. Leukopenia was defined as leukocytes $<2.0\times10^9$/l, leading to temporary discontinuation of treatment. The patient resumed treatment with unaltered dose and schedule after the temporary withdrawal. Toxicity was evaluated in all treated patients. Antineoplastic response was evaluated only in patients treated during at least 4 weeks after entry.

Pharmacokinetics. Four patients were included in the pharmacokinetic study. Two patients were followed for up to 24 h and 2 patients to 72 h. Plasma was sampled at t=0, 30 min, and 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 55, and 72 h. Fractionated urine was collected in the 2 patients followed for 72 h. Samples were frozen at −80°C until analysis. Plasma extraction: Stock aqueous solution of doxorubicin hydrochloride 50 µl and phosphate buffer, pH 8.3, 1 ml were added to plasma samples in polypropylene tubes. The mixture was extracted with 7 ml chloroform/isopropanol 4 : 1 by whirl mixing for 50 s and centrifuged at 2000 rpm for 10 min. The organic layer was transferred into another polypropylene tube and extracted with 500 µl 0.2 M phosphoric acid. The acid phase was removed and washed with 2 ml n-hexane. Standard curves were prepared daily by extracting plasma spiked with known amounts of 4-dm DNR and 4-demethoxydaunorubicinol (4-dmDNR-ol). 200 µl was injected into the chromatographic system. Urine was diluted with phosphoric acid and 20 µl was injected. The chromatographic system consisted of a Waters 6000 A solvent delivery system, a Waters U6K injector and a Hitachi F 1000 spectrofluorescence detector (excitation/emission wave lengths 470/550 nm). The column was a Chromosep 3×100 mm filled with ChromSpher C8 5 µm. The mobile phase consisted of acetonitrile 35% and KH2P04 6.8 g/l adjusted to pH 3 with phosphoric acid 65%. The flow rate was 0.4 ml/min and the limit of detection was 0.25 ng/ml for both the parent compound and the metabolite.

The terminal half-lives of 4-dm DNR and 4-dm DNR-ol were calculated by a computerized least-square fitting program. The renal clearance (Clr) was calculated by dividing the amount recovered in the urine (0–72 h) by the area under the plasma concentration curve (AUC: 0–72 h) calculated by the trapezoidal rule.

Results

The 51 patients received a total of 552 courses of drug therapy (Table 2) (median 11 courses, range 1–36) over a median of 12 weeks (range 1–36) with a median cumulated dose of 270 mg 4-dm DNR (range 15–660 mg).

Table 1

Patient characteristics

Characteristics	No. of patients
Total	51
Male/female	23/28
Age median (range) 56 years (19–74)	
Performance status (WHO): median (range) 1 (0–4)	
Prior treatment	46
Surgery	46
Chemotherapy	7
Radiotherapy	21
Chemotherapy and radiotherapy	4
Disease	
Gastrointestinal tract	35
Head–neck	6
Breast	4
Other	6

Drug toxicity could be evaluated in 49 patients and tumor response in 44 patients. Two patients (dose levels 22.5 and 20.0 mg/m^2) died from progressive disease after 1 and 2 weeks respectively. There were no cases of complete or partial remission, stable disease was reported in 13 patients with a median duration of 12 weeks (range 4–23). Disease progression was observed in 31 patients.

No patients were hospitalized for drug-induced septicemia or fever, and no deaths were supposed to be drug-related. Table 2 shows the number of patients within the various dose groups: 3 patients were treated at each dose level including 17.5 mg/m^2, at each level 20.0, 22.5 and 25.0 mg/m^2 more than 7 patients were included. Leukocytes dropped to the lowest value of 0.5×10^9 cells/l in only one patient after 3 courses of therapy at a dose level of 22.5 mg/m^2, and was followed by postponement of treatment for 2 weeks. Treatment was discontinued (Table 2) due to anorexia and malaise in one patient at a dose level of 15.0, 17.5 and 25.0 mg/m^2 respectively, and in 3 patients at a dose level of 22.5 mg/m^2. No patient discontinued treatment due to leukopenia.

Table 3 shows the time in weeks between the very first treatment to the first, second and third leucopenia episode and the time to toxic non-hematologic episode. Leucopenia was observed in 2 of 7 patients at a dose level of 20 mg/m^2 and in 8 of 11 patients at a dose level of 22.5 mg/m^2. Leucocyte counts were normalized within one week after 21 episodes, 2 weeks in 5 episodes, whereas only one episode lasted 3 weeks.

Thrombocytopenia was not observed at the used dose levels, and no drop in hemoglobin level was noted that could be related to the treatment.

Nausea and vomiting, which usually began several hours after drug administration and lasted 4–6 h, was

Table 2

Phase I study of 51 patients treated with 4-demethoxydaunorubicin

Dose of 4-dm DNR mg/m² (No. of patients)	Cumulated dose mg Median (range)	No. of courses Median (range)	Cause of treatment stop* (No. of patients)	B-leucocytes $\times 10^9$/l Initial; median (range) during treatment
2.5 (3)	45 (15–55)	9 (3–12)	PD (3)	6.6; 7.5 (5.0–12.0)
5.0 (4)	330 (90–360)	33 (18–36)	PD (4)	7.9; 6.1 (3.6–26.0)
7.5 (3)	120 (80–150)	12 (8–15)	PD (3)	7.1; 8.5 (4.3–13.3)
10.0 (3)	260 (80–260)	13 (4–12)	PD (3)	6.1; 6.1 (5.2–11.2)
12.5 (3)	250 (120–275)	10 (6–11)	PD (3)	7.0; 10.9 (2.4–28.2)
15.0 (3)	275 (200–460)	11 (8–23)	max (1), tox (1), PD (1)	5.9; 4.3 (1.9–20.0)
17.5 (3)	360 (300–660)	12 (10–22)	max (1), tox (1), PD (1)	7.1; 4.4 (1.1–15.2)
20.0 (10)	370 (60–600)	11 (2–18)	max (4), PD (6)	9.7; 5.8 (1.4–15.2)
22.5 (12)	220 (35–540)	6 (1–14)	max (1), tox (3), PD (8)	6.3; 3.8 (0.5–18.6)
25.0 (7)	360 (100–640)	8 (2–18)	max (2), tox (1), PD (4)	7.0; 4.3 (1.5–16.3)

* max: maximum dose; tox: toxicity; PD: progressive disease.

Table 3

Leukopenia episodes and non-hematologic toxicity

Dose level mg/m²	Weeks to first leukopenia episode		Weeks to second leukopenia episode		Weeks to third leukopenia episode		Weeks to toxic non-hematologic episode	
	Median (Range)	No. of episodes/ patients at risk	Median (Range)	No. of episodes/ patients at risk	Median (Range)	No. of episodes/ patients at risk	Median (Range)	No. of episodes/ patients at risk
2.5	–		–		–		–	
5.0	–		–		–		4 (4)	1/3
7.5	–		–		–		–	
10.0	–		–		–		–	
12.5	–		–		–		–	
15.0	8 (8)	1/3	12 (12)	1/2	–		20 (20)	1/1
17.5	8 (8)	1/3	16 (16)	1/1	–		12 (12)	1/2
20.0	10 (7–12)	2/7	14 (13–15)	2/5	–		–	
22.5	4 (2–5)	8/11	7 (6–14)	4/9	11 (11)	1/5	9 (3–17)	4/10
25.0	4 (4–5)	3/6	11 (8–14)	2/5	12 (12)	1/4	–	

observed at 20.0 mg/m² and was more intensive at 22.5 mg/m² and 25.0 mg/m². Nausea and vomiting was effectively relieved by antiemetics. Anorexia and malaise lasted longer than nausea and vomiting, and with each new course of therapy the symptoms tended to become more pronounced and prolonged. These side effects were only registered in patients receiving more than 12.5 mg/m², thus mild symptoms occurred at a dose level of 15 mg/m², whereas moderate and severe complaints were experienced in those at 17.5 and at 20.0 to 25.0 mg/m² respectively.

No patient developed cardiac dysfunction to judge from clinical examination or evaluated by ECG and ejection fraction (MUGA). Renal toxicity was not observed and Cr-EDTA clearance and plasma creatinine remained normal. No drug-induced hepatotoxicity was observed. A rise in serum bilirubin and alkaline phosphatases was observed in some patients with progressive hepatic metastasis but was probably not related to treatment. No other toxicity was observed.

The results of the pharmacokinetic analysis are shown in Table 4. Plasma samples from the 2 patients followed for 72 h allowed estimation of the terminal half-lives of 4-dm DNR and its metabolite 4-dm DNR-ol. The higher plasma concentration (Cmax) and longer $t_{1/2}$ of the metabolite resulted in an area under the concentration curve

Table 4

Pharmacokinetics of 4 patients treated weekly with oral 4-demethoxydaunorubicin

Patient No.	Dose level mg/m²	Cmax ng/ml	Tmax h	AUC ng×h/ml	Clr ml/min	$t_{1/2}$ h
4-demethoxydaunorubicin						
1[a]	22.5	13	3	–	–	–
2[a]	22.5	27	2	–	–	–
3[b]	22.5	11	4	140	51	16
4[b]	25.0	7	3	107	74	26
4-demethoxydaunorubicinol (metabolite)						
1[a]	22.5	48	4	–	–	–
2[a]	22.5	56	3	–	–	–
3[b]	22.5	42	7	2 440	52	57
4[b]	25.0	20	3	1 428	74	52

Clr = renal clearance.
[a] 24 h
[b] 72 h

more than 10 times higher than that of the parent compound. The figure shows the plasma concentration vs. time curve in one patient.

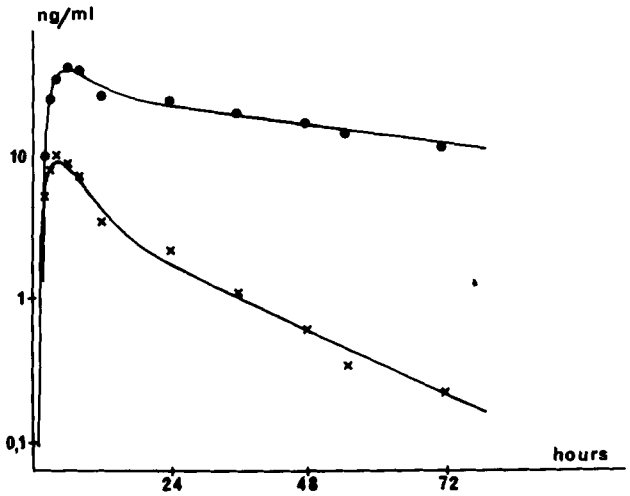

Figure. Plasma concentrations of drug 4-dm DNR (✕–✕–✕) and metabolite 4-dm DNR-ol (●–●) vs. time plot in patient No. 3, treated with a single dose of 4-demethoxydaunorubicin 22.5 mg/m² by oral route of administration.

Discussion

The antineoplastic anthracycline 4-dm DNR can be administered orally and its bioavailability is approximately 30%. This figure was increased to 54% when also the metabolite 4-dm DNR-ol was considered (7).

4-dm DNR may be administered weekly to increase the dose intensity. With a 3-week schedule (2) the maximum dose tolerated was 45 mg/m², corresponding to a weekly dose of 15.0 mg/m².

In the present study no toxicity was seen at weekly doses less than 15 mg/m². The dose-limiting factors were leukopenia, anorexia and malaise. The observation of anorexia and malaise is important; it will presumably interfere with patient acceptance.

Our pharmacokinetic results are in agreement with those of other investigators (8). We conclude from the identical renal clearance rates of parent compound and metabolite (Table 4) that the differences in half-lives could not be ascribed to differences in renal handling. In another study, the renal clearance of doxorubicin was found to be of the same magnitude (6). The variability in drug absorption and the therapeutic effect of the metabolite indicate that future clinical trials concerning 4-dm DNR should include pharmacokinetic monitoring.

In a phase I study utilizing a weekly schedule of oral 4-dm DNR for 4 consecutive weeks followed by a rest period of 3 weeks to pretreated patients, Dodion et al. (4) reported leukopenia as the dose-limiting factor at dose levels of 15.0–17.5 mg/m². In that study by Dodion et al., where only few patients tolerated a third and a fourth dose of 17.5 and 20.0 mg/m², higher doses were only administered 2 weeks in a row, and with this schedule the dose-limiting factor was leukopenia at a dose level of 25.0 mg/m². Dodion et al. also found that myelosuppression was highly variable and could not be related to prior therapy, bone or liver metastases or performance status. The erratic myelosuppression was suggested to depend on unreliable bioavailability. The phase I study of Dodion et al. is inconclusive with regard to tolerated dose in a weekly schedule.

The difference between the dose intensity of weekly 4-

dm DNR, which was 20 mg/m^2 in our study and 10 mg/m^2 in the study of Dodion et al. (4), is probably due to the heavy pretreatment of the predominating 'bad risk' patients in the latter study.

In future phase II studies with 4-dm DNR, using a weekly schedule, we recommend the application of an initial dose of 20.0 mg/m^2, increasing to 22.5 or even 25.0 mg/m^2 after 4 weeks' pending absence of toxicity.

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