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Phase I Clinical and Pharmacokinetic Trial of Oral Menogaril Administered on Three Consecutive Days*†‡

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Abstract—*Eighteen adult patients with solid tumors were treated with oral menogaril, a new anthracycline antibiotic active against human breast cancer after intravenous administration. The drug was given orally on 3 consecutive days every 4 weeks at doses ranging from 50 to 175 mg/m²/day. Reversible and dose-related leukopenia was the dose-limiting toxicity. Thrombocytopenia was less frequent. Hematologic toxicity was maximal usually 2 weeks after treatment and recovery usually occurred within 4 weeks. At doses from 50 to 150 mg/m²/day, non-hematologic side-effects of oral menogaril were infrequent and mild and consisted of nausea and vomiting (one patient), alopecia (two patients), mucositis (two patients) and liver function test abnormalities (three patients). The single patient treated at a daily dose of 175 mg/m²/day developed grade IV leucothrombocytopenia, with fever and gastrointestinal bleeding. This was followed by heart failure and the patient died from multisystem organ failure. Peak plasma concentrations of menogaril ranged from 0.043 to 0.409 μM and were linearly correlated with the dose. Similarly, the area under the plasma concentration versus time curve varied from 0.33 to 9.59 μM × h and was linearly correlated with the dose. The mean harmonic half-life was 11.3 ± 6.4 h. A comparison of the data from the present trial and our previous study with intravenous menogaril indicates a bioavailability of 32 ± 12%. There was an excellent relationship between the white blood cell decrease (as a percentage of the pretreatment value) and several pharmacokinetic parameters; the best correlation was obtained with the plasma concentration of menogaril at 4 h after treatment. A dose of 150 mg/m²/day for 3 consecutive days is recommended for phase II trials with oral menogaril but the bioavailability of the drug should be monitored carefully and, more specifically, the concept of a pharmacokinetic adjustment of the dose of menogaril should be evaluated prospectively.*

INTRODUCTION

THE ANTHRACYCLINE antibiotics are among the most widely used antineoplastic agents. However, their clinical use may be limited by the occurrence of several side-effects, among which cardiac toxicity is one of the most disturbing. Therefore, there has been a continuous search for new anthracycline antibiotics with better therapeutic indices.

Menogaril (NSC 269148) was brought to clinical trials based on a broad spectrum of antitumor activity against experimental murine tumors, a mechanism of action possibly different from that of doxorubicin, a reduced cardiotoxicity in animal models and the demonstration of antitumor activity after oral administration in animal models [1]. Phase I trials with intravenous menogaril showed that leukopenia was the dose-limiting toxicity [2–7]. The most important non-hematologic side-effects consisted of phlebitis and erythema. Otherwise, the drug was well tolerated. The maximum tolerated doses ranged between 250 and 300 mg/m² depending on the schedule. Phase II clinical trials with intravenous menogaril are ongoing in Western Europe and North America; definite antitumor

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Table 1. *Patient characteristics* (n = 18)

Characteristics	Value
Median age (range)	56 (36–70)
Median PS (ECOG) (range)	2 (0–2)
Male/female	11/7
Prior treatment	17
Radiotherapy	11
Chemotherapy (anthracyclines)	17 (4)
Solid tumors	18
Head and neck	6
Colorectal	2
Melanoma	2
Others	8

activity has been shown against breast cancer [8, 9].

Since menogaril retains antitumor activity after oral administration in animals and since the drug has demonstrated antitumor activity after intravenous administration in man, the next logical step in the clinical development of menogaril was to investigate the oral administration of the drug. The present study was undertaken to characterize the toxicity and define the maximum tolerated dose after oral administration of menogaril on 3 consecutive days. This schedule was preferred over a single oral administration because fractionation of the dose was associated with reduced gastrointestinal toxicity for idarubicin, another anthracycline antibiotic that can be administered orally [10]. In addition, since the cardiac toxicity of anthracycline antibiotics is thought to be related to the peak plasma concentration, fractionation of the dose would result in a further reduction of the cardiotoxic potential of menogaril [11].

MATERIALS AND METHODS

Patient selection

A total of 18 patients with histologically confirmed solid malignancies no longer amenable to conventional therapy were entered into this study (Table 1). They had a performance status ≤2 on the Eastern Cooperative Oncology Group (ECOG) scale and a life expectancy of at least 6 weeks. Neither chemotherapy nor radiation therapy had been administered for at least 4 weeks before entry into the study (this time span was increased to 6 weeks for therapy with nitrosoureas or mitomycin). The patients had recovered from the toxic effects induced by previous therapy (with the exception of alopecia). Prior therapy with anthracycline antibiotics was allowed provided that the total dose of anthracycline antibiotics did not exceed 250 mg/m^2. All patients had normal renal (serum creatinine <1.5 mg/dl), hepatic (bilirubin level <1.5 mg/dl) and hematologic (WBC >4000 μl, platelets >100,000/μl) functions. No patients had major intercurrent disease. Cardiac diseases were excluded by history, physical examination and ECG, and whenever indicated, by echocardiography and isotopic ejection fraction. All patients gave their informed consent before entry into the study.

Treatment

Menogaril was supplied by the Upjohn Company (Kalamazoo, Michigan) in vials containing 50 mg of menogaril, 100 mg of mannitol and 16.6 mg of lactic acid. The vials were reconstituted in 2.5 ml of sterile water and further diluted in grapejuice to yield a final concentration of 5 mg/ml. In preliminary experiments, grapejuice was found to produce the solution with the most acceptable taste. The treatment plan consisted of the oral administration of menogaril on 3 consecutive days every 4 weeks. The starting dose was 50 mg/m^2/day or 150 mg/m^2/course, which corresponds to one half of the maximum tolerated dose of menogaril after intravenous administration in 3 consecutive days. In the absence of toxicity, three evaluable patients were entered per dose level and the dose was escalated by increments of 50 mg/m^2/day. At the second dose level (100 mg/m^2/day), signs of toxicity were encountered; more patients were entered and further dose escalation consisted of steps of 25 mg/m^2/day. Retreatment in a given patient was allowed if all eligibility criteria were still satisfied. Four patients who did not experience any toxicity were retreated at a higher dose. One patient was retreated at a lower dose because of disease-related liver test abnormalities. For the other retreated patients, the same dose was administered. Overall, 31 courses were administered: nine patients received one course of therapy, five received two courses, and four, three courses.

Follow-up studies

Observation included weekly history and physical examination; complete blood cell counts were obtained twice weekly and a SMA-12 chemistry panel weekly. In patients with measurable disease, tumor response was assessed according to conventional criteria [12].

Pharmacokinetic study

A pharmacokinetic study was performed during 12 courses in 10 patients. Ten milliliter samples of heparinized venous blood were obtained at the following times: 0 (baseline), 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48 and 72 h after the first oral dose. Blood samples were immediately centrifuged and the plasma was stored at −20°C until analysis. Menogaril was assayed using a minor modification of the high performance liquid chromatography (HPLC) methodology described by McGovren *et al.* [13]. The limit of quantitation was 5 ng/ml. Pharmaco-

Table 2. Drug-induced leukopenia

	Dose (mg/m²/day)				
	50	100	125	150	175
No. of evaluable/toxic patients	3/0	7/4	5/3	5/5	1/1
No. of evaluable courses	6	9	6	6	1
Median WBC nadir (× 1000/μl)	6.7	3.3	3.5	2.3	0.2
Range	5.7–7.1	0.9–6.0	2.5–5.7	1.4–3.0	—
Median day of nadir	—	18	13	13	14
Range	—	15–18	11–15	12–20	—
Median day of recovery	—	23	20	21	29
Range	—	21–32	18–21	19–36	29–38

kinetic modeling of the menogaril plasma concentration time data was performed on MLAB, a non linear fitting program using a 1/concentration squared weighting function [14]. The 0–24 h data were fitted to the following equation:

$$\text{concentration} = A\,(e^{-\alpha t} - e^{-\beta t}).$$

The area under the concentration versus time curve (AUC) corresponding to a single oral administration was calculated by trapezoidal rule until the 24 h time point and then by first-order extrapolation until infinity using the experimentally determined terminal disposition half-life.

RESULTS

Hematologic toxicity

Leukopenia was dose-limiting (Table 2). One patient was not evaluable because of insufficient hematological follow-up; one patient was retreated at reduced dosage because of hepatic insufficiency due to malignant disease and was analysed separately. No patient developed leukopenia at 50 mg/m²/day; approximately one half of the patients developed leukopenia at 100 and 125 mg/m²/day and all patients treated at 150 mg/m²/day developed hematological toxicity. The single patient treated at 175 mg/m²/day developed major leukopenia and fever requiring broad spectrum antibiotics. That patient had a diagnosis of squamous cell carcinoma of the head and neck previously treated with radiotherapy on the cervico-facial area and two courses of chemotherapy with cisplatin and fluorouracil 1 year before receiving menogaril. His performance status prior to entry into the study was 2. For all leukopenic patients, the median day of WBC nadir was 16 (11–20) and the median day to recovery was 22 (18–36); there was no apparent difference in the days of nadir and recovery according to the dose (Table 2).

Thrombocytopenia was less frequent and was observed only in three patients: one at 100 mg/m²/day (nadir: 23,000/μl), one at 125 mg/m²/day (nadir: 84,000/μl) and one at 175 mg/m²/day (nadir: 19,000/μl). The patient treated at 100 mg/m²/day developed petechiae; the one treated at 175 mg/m²/day had gastrointestinal bleeding.

One patient with massive liver metastases received a first course of oral menogaril at a dose of 150 mg/m²/day and developed a white blood cell nadir at 3000/μl with no thrombocytopenia. Because of worsening liver function tests including an elevated bilirubin at 2.9 mg/dl, a second course was given at reduced dosage (100 mg/m²/day). The white blood cell nadir was 7700/μl on day 12 and the platelet nadir 496,000/μl on the same day.

Neutrophil counts followed closely the total white blood cell counts. Anemia was calculated as the difference between the hemoglobin level before treatment and the lowest value after treatment. The hemoglobin drop was lower than 3.0 g/dl in all patients; such variations may be related to spontaneous variations, repeated blood sampling, malignant disease and/or menogaril treatment. There was no sign of hemolytic anemia.

Non-hematologic toxicity

Non-hematologic side-effects were mild (Table 3). Alopecia was grade 1 in all three cases. Upper gastrointestinal toxicity was observed in two patients (mild vomiting in one, prolonged nausea in the other). Two patients had mild diarrhea. Mucositis was limited to mouth soreness or a few mouth ulcers (one patient each). Two patients developed infectious fever; one is the patient treated at 175 mg/m²/day; although no infection was microbiologically documented, he was treated with broad spectrum antibiotics. The other one developed fever while he was leukopenic (WBC nadir: 1400/μl); several blood cultures were positive for *Staphylococcus aureus*. Fever resolved with broad spectrum antibiotics. The patient treated at 175 mg/m²/day developed heart failure 3 weeks after treatment with menogaril. This was complicated by multisystem organ failure and the patient died 31 days after the start of

Table 3. Non-hematological toxicities

Parameter	Dose (mg/m²/day)				
	50	100	125	150	175
No. of evaluable patients	3	9	5	5	1
No. of evaluable courses	7	11	6	6	1
No. of toxic patients*	0	2	2	4(1)	1(1)
Nausea vomiting				1	1
Mucositis			1	1	
Alopecia	0/2†	1/7	0/5	2/3	0/0
Diarrhea		1	1		
Infection				1(1)	1(1)
Bleeding		1			1(1)
Heart failure					1(1)

*In parentheses: cases with WHO grade III–IV toxicity.
†No. of patients with alopecia/No. of patients evaluable for this side-effect.

Table 4. Pharmacokinetic parameters

Parameter	Unit	Dose (mg/m²/day)					
		50 $n = 3$	100 $n = 3$	125 $n = 3$	150 $n = 2$	175 $n = 1$	all $n = 12$
Peak concentration	μM	0.071	0.100	0.148	0.206	0.409	—
Range		0.051–0.089	0.051–0.162	0.043–0.297	0.146–0.266	—	
AUC*	μM × h	1.38	2.05	2.31	7.61	9.59	—
Range		1.04–1.71	0.72–3.01	0.33–3.77	6.64–8.59	—	
Terminal half-life†	h	11.5	12.8	7.5	20.2	15.5	11.3
Range		9.3–13.5	10.5–25.0	4.7–10.6	17.9–23.9	—	4.7–25.0
Bioavailability‡	%	25.5	24.8	24.1	46.3	50	32.2
Range		19.0–31.2	22.2–27.4	22.2–27.5	40.4–52.2	—	19.0–50.0

*Area under the plasma concentration versus time curve (after a single day administration).
†Harmonic mean.
‡Excluding the two courses of the patient under phenobarbital.

treatment with menogaril. Cardiomegaly and severe coronary atheromatosis were found at autopsy; microscopic examination of the heart did not reveal specific findings. This patient had a past history of alcoholism.

Four patients developed abnormalities of liver enzymes. The first one is the patient treated at 175 mg/m²/day: he developed a grade IV increase of transaminases and LDH and grade I increase of alkaline phosphatase. The serum bilirubin increased slightly although it remained within normal limits. These abnormalities appeared concomitantly with the development of heart failure. Three other patients (one at 50 mg/m²/day, two at 100 mg/m²/day) developed grade I elevation of liver enzymes (LDH in two, alkaline phosphatase in one).

Fifteen patients had measurable lesions and were evaluable for response. No patient responded to the treatment.

Pharmacokinetic study

The peak plasma concentration of menogaril (Table 4) ranged from 0.043 to 0.409 μM and was linearly correlated with the dose (correlation coefficient: 0.694; $P < 0.02$); the AUC ranged from 0.33 to 9.59 μM × h and was also linearly correlated with the dose (correlation coefficient: 0.768; $P < 0.005$). One patient was under treatment with phenobarbital for epilepsy when she received menogaril; she had very low plasma concentrations of the drug. Excluding the two courses received by this patient improves the correlation between dose and peak plasma concentration (correlation coefficient: 0.788; $P < 0.01$). For the correlation between AUC and dose, the correlation coefficient becomes 0.895 ($P < 0.001$). The mean harmonic terminal half-life was 11.3 ± 6.4 h with apparently no variation with the dose (Table 3). The half-lives for the two courses of the patient under phenobarbital were 10.5 and 4.7 h, respectively. These values are not statistically different from the mean half-life of the rest of the population.

The bioavailability was estimated by comparing the data of the present trial with those of our previous intravenous trial [2]. The AUCs after a single intravenous administration were normalized

for an arbitrary dose of 100 mg/m^2. The mean value was 11.0 ± 3.4 μM × h. Similarly, for each patient included in the oral trial, the AUC corresponding to a single oral dose was estimated by trapezoidal rule using the 0–24 h time points and then by extrapolation until infinity using the experimentally determined half-life. The AUC was then normalized for an arbitrary dose of 100 mg/m^2. For each patient, bioavailability was calculated as the ratio as a percentage of his normalized AUC divided by the mean normalized AUC after intravenous administration. The patient under phenobarbital had, for each of his two courses, a very low bioavailability (6.6 and 3.0%, respectively) and was excluded from further analysis. The values for the other patients are listed in Table 4. The mean bioavailability was 32 ± 12%.

The relationships among the white blood cell decrease in percent of the pretreatment value (%DWBC) and pharmacokinetic parameters (x) were investigated according to two equations:

exponential: $\%\text{DWBC} = 100(1-e^{-ax})$

Hill: $\%\text{DWBC} = \dfrac{x^a}{b^a + x^a}$.

To evaluate the validity of these relationships, the predicted %DWBC were compared by linear regression analysis with the actually observed %DWBC. The same methodology was used to study the relationships among the polyneutrophil decrease as a percentage of the pretreatment value (%DPN) and pharmacokinetic parameters. The relationship between the AUC and %DWBC is illustrated in Fig. 1; the correlation coefficients between predicted and observed %DWBC were 0.813 ($P \leqslant 0.005$) and 0.827 ($P \leqslant 0.001$) for the exponential and Hill equations, respectively. There were also good relationships among % DWBC and the plasma concentration of menogaril at 2, 3 and 4 h after treatment. The best relationship was obtained between the plasma concentration of menogaril at 4 h after treatment and the %DWBC (Fig. 2); the correlation coefficients were 0.842 ($P \leqslant 0.001$) and 0.842 ($P \leqslant 0.001$) for the exponential and Hill equations, respectively.

The relationships among pharmacokinetic parameters and %DPN were less satisfactory than with the %DWBC. For example, when AUC was used as pharmacokinetic parameter, the correlation coefficients between predicted and observed %DPN were 0.763 ($P \leqslant 0.005$) and 0.763 ($P \leqslant 0.005$) for the exponential and Hill equations, respectively. The best relationship was obtained for the plasma concentration at 2 h after treatment ($r = 0.808$ for both the exponential and Hill equations; $P \leqslant 0.005$).

DISCUSSION

The purpose of this study was to define the maximum tolerated dose of menogaril after oral administration on 3 consecutive days. The major toxicity observed in this trial was myelosuppression with leukopenia being more important than thrombocytopenia. Leukopenia was predictable, dose-related and reversible. The median WBC nadir at 150 mg/m^2/day was 2300/μl with a range from 1400 to 3000 and we think that this dose should be recommended for phase II trials with oral menogaril. The single patient treated at 175 mg/m^2/day developed major leukopenia and thrombocytopenia with infectious fever and bleeding, followed by heart insufficiency, and died of multisystem organ failure. This happened despite the fact that the patient had received minimal prior therapy (cervicofacial radiotherapy and two courses of chemotherapy with cisplatin and fluorouracil) and had an acceptable starting performance status of 2. Pharmacokinetic analyses in that patient showed disproportionately high plasma levels and a bioavailability higher than in all but one patients. The accrual of more patients at 175 mg/m^2/day would have allowed one to define more precisely the hematological toxicity at this dose level but would have been difficult to justify ethically.

Oral menogaril was otherwise very well tolerated. This treatment modality avoided completely the skin toxicity described after intravenous administration [2–7]. Alopecia, mucositis, diarrhea and abnormalities of the liver function tests were mild and observed in small numbers of patients. Gastrointestinal tolerance was also remarkably good with our schedule. In contrast, at the Cancer Center of San Antonio, where menogaril was given as a single oral dose [15], the maximum tolerated dose was 625 mg/m^2 and at that dose, gastrointestinal toxicity was difficult to control with antiemetics. Although one should be careful in comparing trials from different institutions, our schedule may be better tolerated as far as gastrointestinal tolerance is concerned; this confirms our initial hypothesis regarding the influence of dose fractionation on gastrointestinal toxicity.

The development of heart failure in the patient who received menogaril at the dose of 175 mg/m^2/day is disturbing even though alcoholic cardiomyopathy and coronary artery disease may have been contributing factors. In our phase I trial with intravenous menogaril, several patients developed acute arrhythmias, but no patient developed symptoms or signs of cardiac failure [2]. Similarly, to our knowledge, only four out of the 157 patients treated in the phase I trials reported in the literature [2–7] developed a ⩾10% drop of their left ventricular ejection fraction and there was no case of overt heart failure. However, in phase I trials, patients are

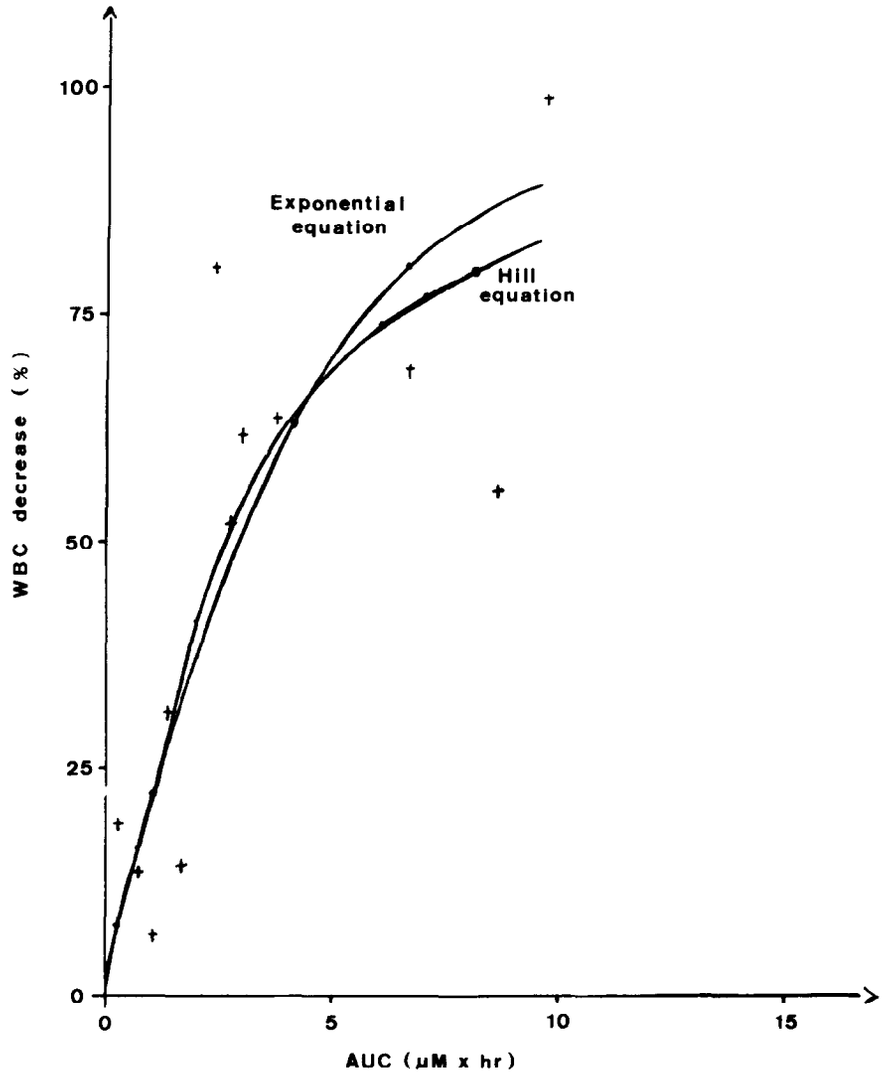

Fig. 1. Relationship between the area under the plasma concentration of menogaril versus time curve and the white blood cell decrease as a percentage of the pretreatment value. The mathematical equations are described in the 'Results' section. Each point represents an individual patient.

treated for short periods of time. A better characterization of the chronic cardiotoxicity of menogaril will require the observation of a larger number of patients treated for longer periods of time and monitored by sophisticated methods such as isotopic ejection fraction or endomyocardial biopsies.

Pharmacokinetic analysis showed that menogaril was the only fluorescent compound detected in plasma. Peak plasma concentrations and area under the curve were linearly related with the dose. The terminal disposition half-life was somewhat shorter in this trial than in our phase I trial with intravenous menogaril. However, the terminal half-life may have been artificially shortened in this study by the fact that its calculation took into account only the plasma concentrations up to 24 h. The historical comparison of the area under the curve obtained in this study with those obtained in our phase I trial with intravenous menogaril reveals a bioavailability of 32 ± 12%. This value is somewhat lower than the ratio of the recommended dosages for phase II trials [200/(150×3) = 44%). As discussed above, the terminal half-life may have been underestimated in our oral study; this would lead to an underestimation of the area under the curve after oral administration and of the bioavailability. These considerations may explain the discrepancy between the bioavailability based on the ratio of the AUCs and that based on the ratio of recommended doses for phase II studies. In another trial, two patients received menogaril orally or intravenously in consecutive order: the bioavailability was 40% [16]; 30 patients were evaluated in an interstudy comparison and a bioavailability of 30 ± 13% was found. These data are consistent with ours.

Our data confirm that there is a relationship among pharmacokinetic parameters and hematologic data, as first demonstrated by Egorin *et al.*

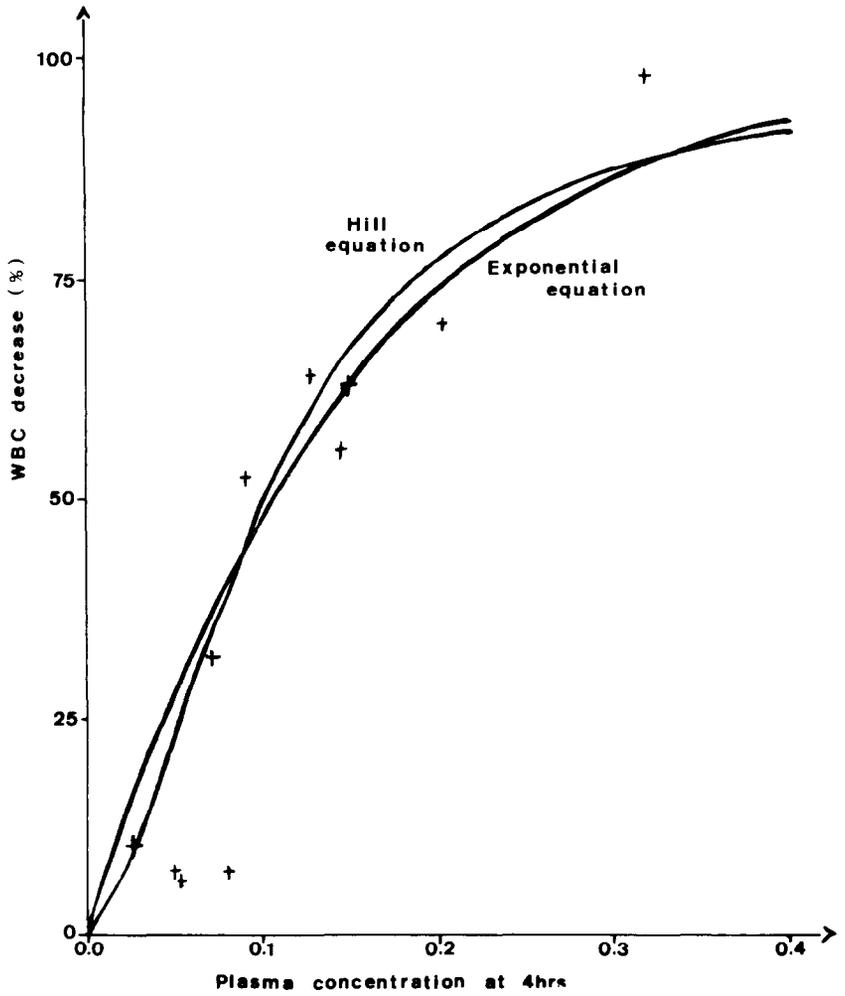

Fig. 2. Relationship between the plasma concentration of menogaril at 4 h *after treatment and the white blood cell decrease as a percentage of the pretreatment value. The mathematical equations are described in the 'Results' section. Each point represents an individual patient.*

[17]. The relationship between the white blood cell decrease (as a percentage of pretreatment value) and the area under the plasma concentration versus time curve were adequately described by an exponential equation or the Hill equation. In addition, a similar relationship was detected between the percentage white blood cell decrease and the plasma concentration of menogaril at 4 h after treatment. The latter observation gives the possibility of adjusting the dosage of menogaril to the characteristics of each individual patient: an arbitrary dose could be given on day 1 to determine the individual bioavailability. The dosage on days 2 and 3 could then be adjusted according to the individual bioavailability and the desired degree of myelosuppression.

In conclusion, oral menogaril given on 3 consecutive days is very well tolerated. Phase II studies are indicated to determine the activity of oral menogaril, mainly in breast cancer since antitumor activity in this disease was demonstrated after intravenous administration. These studies should be conducted along with careful pharmacokinetic monitoring in order to ascertain proper dosage in each individual patient; finally, the concept of individual adjustment of the dose should be validated in well designed prospective studies.

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