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PHASE I CLINICAL 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/m^2/day. Reversible and dose-related leukopenia was the dose-limiting toxicity. At doses from 50 to 150 mg/m^2/day, non-hematologic side effects of oral menogaril were unfrequent and mild and consisted of nausea and vomiting (1 patient), alopecia (2 patients), mucositis (2 patients) and liver function test abnormalities (3 patients). The only patient treated at a daily dose of 175 mg/m^2 developed grade IV leukothrombocytopenia, with fever and gastrointestinal bleeding. This was followed by heart insufficiency and the patient died from multisystem organ failure. A dose of 150 mg/m^2/day for 3 consecutive days is recommended for phase II trials with oral menogaril.

Key words: Chemotherapy, phase I study; menogaril, solid tumors.

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 (9). Phase I trials with intravenous menogaril showed that leukopenia was the dose-limiting toxicity (2, 4, 5, 8, 11, 13). 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/m^2 depending on the schedule. Phase II clinical trials with intravenous menogaril are ongoing in Western Europe and North America; definite antitumor activity has been shown against breast cancer (6, 10).

Since menogaril retains antitumor activity after oral administration to animals and since the drug has demonstrated antitumor activity after intravenous administration to man, the next logical step in the clinical development of menogaril was to investigate the oral adminstration 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 adminstration because fractionation of the dose was associated with reduced gastrointestinal toxicity for idarubicin, another anthracycline antibiotic that can be administered orally (3). In addition, since the cardiac toxicity of anthracycline antibiotics is considered to be related to the peak plasma concentration, fractionation of the dose would result in a further reduction of the cardiotoxic potential of menogaril (7).

Material and Methods

Patients' selection. A total of 18 patients with histologically confirmed solid malignancies no longer amenable to conventional therapy entered into this study (Table 1). They had a performance status ≤ 2 in the Eastern Cooper-

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ative 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 <15 mg/l), hepatic (bilirubin level <15 mg/l), and hematologic (WBC >4000/μl, platelets >100000/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. 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 abscence of toxicity, 3 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: 9 patients received 1 course of therapy, 5 received 2 courses, and 4 patients 3 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 measureable disease, tumor response was assessed according to conventional criteria (12).

Results

Hematologic toxicity. Leukopenia was dose-limiting (Table 2). No patient developed leukopenia at 50 mg/m^2/day; approximately one half of the patients developed leukopenia at 100 and 125 mg/m^2/day and all patients treated at 150 mg/m^2/day developed hematological toxicity. The single patient treated at 175 mg/m^2 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 cervicofacial area and 2 courses of chemotherapy with cisplatin and fluorouracil one 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, 22 (18–36); there was no apparent differences in the days of nadir and recovery according to the dose (Table 2).

Table 1

Patients' characteristics (n=18)

Characteristics	Value
Median age (range)	56 (36–70)
Median performance status (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

Thrombocytopenia was less frequent and was observed only in 3 patients: one at 100 mg/m^2/day (nadir: 23000/μl), one at 125 mg/m^2/day (nadir: 84000/μl) and one at 175 mg/m^2 (nadir: 19000/μl). The patient treated at 100 mg/m^2/day developed petechiae; the one treated at 175 mg/m^2/day had gastrointestinal bleeding.

Non-hematologic toxicity. Non-hematologic side effects were mild (Table 3). Alopecia was grade 1 in all 3 cases. Upper gastrointestinal toxicity was observed in 2 patients (mild vomiting in one, prolonged nausea in the other). Two patients had mild diarrhea. Mucositis was limited to mouth soreness or to a few mouth ulcers (1 patient each). Two patients developed infectious fever: one is the patient treated at 175 mg/m^2/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/m^2/day developed heart insufficiency 3 weeks after treatment with menogaril. This was complicated by multisystem organ failure and the patient died 31 days after the start of 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.

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 (×1 000/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

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[a]	0	2	2	4 (1)	1 (1)
Nausea vomiting				1	1
Mucositis			1	1	
Alopecia	0/2[b]	1/7	0/5	2/3	0/0
Diarrhea		1	1		
Infection				1 (1)	1 (1)
Bleeding		1			1 (1)
Heart insufficiency					1 (1)

[a] Cases with WHO grade III–IV toxicity.
[a] No. of patients with alopecia/No. of patients evaluable for this side effect.

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 insufficiency. The remaining three patients (one at 50 mg/m²/day, 2 at 100 mg/m²/day) developed grade I elevation of liver enzymes (LDH in 2, alkaline phosphatase in 1).

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

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/m²/day was 2 300/μl with a range from 1 400 to 3 000 and we think that this dose should be recommended for phase II trials with oral menogaril. The patient treated at 175 mg/m²/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 2 courses of chemotherapy with cisplatin and fluorouracil) and had an acceptable starting performance status of 2.

Oral menogaril was otherwise very well tolerated. This treatment modality avoided completely the skin toxicity described after intravenous administration (2, 4, 5, 8, 11, 13). 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, menogaril was given as a single oral dose (1); the maximum tolerated dose was 625 mg/m². At that dose gastrointestinal toxicity was difficult to control with antiemetics. Our schedule may therefore 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/m²/day is disturbing even though alcoholic cardiomyopathy and coro-

nary artery disease may have been contributing factors. In our phase trial with intravenous menogaril, several patients developed acute arrhythmias, but no patient developed symptoms or signs of cardiac failure (4). Similarly, to our knowledge only 4 out of the 157 patients treated in the phase I trials reported in the literature (2, 4, 5, 8, 11, 13), developed a $\geq 10\%$ drop of their left ventricular ejection fraction and there was no case of overt heart insufficiency. However, in phase I trials patients are treated for short periods of time. A better characterization of chronic cardiotoxicity of menogaril will require an 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.

In conclusion oral menogaril given on 3 consecutive days is a very well tolerated compound. 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.

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