REPORTS

Phase II Study of Intravenous Menogaril in Patients With Advanced Breast Cancer[1,2]

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Menogaril was administered to 40 patients with advanced breast cancer who had not received anthracycline drugs previously. The drug was given iv as a 2-hour infusion, repeated every 4 weeks, at doses of 200 mg/m² and 160 mg/m² in good-risk and poor-risk patients. The overall response rate was 22% in patients with no prior chemotherapy and 10% in patients previously exposed to chemotherapy. Leukopenia was generally moderate and predictable. Phlebitis and erythema along the vein injected occurred in 34% and 17% of the cases, respectively. Menogaril is an active drug used in the treatment of patients with advanced breast cancer who have not had prior systemic therapy. [J Natl Cancer Inst 1988;80:1066-1069]

Menogaril, a semisynthetic analog of nogalamycin, was selected for clinical studies because of its significant antitumor activity against the iv inoculated P388 leukemia and the colon 38 carcinoma in mice (*1*). When compared with doxorubicin, menogaril was 5-10 times less potent in murine tumors, but $\frac{1}{15}$ less potent in inducing cardiotoxicity in the chronic rabbit model (*2*). A different mechanism of action and a cellular uptake greater than that of doxorubicin were also demonstrated (*3*).

When given as a single infusion repeated every 4 weeks, the dose-limiting toxicity was leukopenia; the recommended doses for phase II studies were 200 mg/m² and 160 mg/m² in good-risk and poor-risk patients, respectively (*4*). The main nonhematologic toxicity was a dose-dependent erythema and phlebitis at the injection site, a side effect that became dose limiting when the drug was administered as a 72-hour infusion (*5*).

The Early Clinical Trials Group initiated a phase II study with menogaril given on a single intermittent schedule to patients with advanced breast cancer because of its potential superiority to doxorubicin in therapeutic index.

Patients and Methods

Both previously treated and untreated patients with recurrent and/or metastatic breast cancer were eligible for this study. Eligibility criteria included lesions that could be measured or evaluated with documented progression within the last 2 months; World Health Organization (WHO) performance status ≤ 2; age ≤ 75 years; and no chemotherapy, hormone therapy, or radiation therapy in the previous 4 weeks. The protocol also called for adequate hematologic (wbc count $\geq 4.0 \times 10^3$ μL, platelet count $\geq 100 \times 10^3/\mu$L), hepatic (serum bilirubin $\leq$ 25.6 mmol/L) and renal (serum creatinine $\leq$ 132 mmol/L) function tests. Informed consent was obtained according to local regulations. Patients with prior anthracycline treatment or > 2 previous chemotherapeutic regimens were excluded. Further criteria for exclusion were: brain metastases; ascites, pleural effusions, and osteoblastic bone metastases as the only parameters of disease; and lesions only measurable by ultrasound or computed tomography scan that were not verified by biopsy and with the largest diameter < 5 cm.

Menogaril was administered iv every 4 weeks at doses of 160 mg/m² in poor-risk patients (WHO performance status 2; prior treatment with ≥ 3 myelosuppressive drugs, or with extensive radiotherapy; and diffuse bone metastases) and 200 mg/m² in good-risk patients, respectively. The drug was supplied by Upjohn International, Inc., Brussels, Belgium, in vials of 50 mg of menogaril, 16.6 mg of lactic acid, and 100 mg of mannitol. Each vial was reconstituted with 10 mL of sterile water for a concentration of 5 mg/mL. The total dose was subdivided into three parts, each diluted into 150-200 mL of 5% dextrose just before administration and infused through a large blood vessel over a period of ~30 minutes. The total dose was given over ~2 hours. Later on, in one of the participating centers, the total dose was diluted in 500 mL of 5% dextrose and administered in ~10 minutes. The patient's history and physical examination with an assessment of the lesions that could be evaluated, blood chemistries (including creatinine, bilirubin, SGOT, alkaline phosphatase, and calcium), and an ECG had to be repeated before each cycle. Blood counts were repeated weekly

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during the first 2 months and whenever dose modifications were made. Echographic or isotopic ejection fractions were repeated every 2 cycles in patients who responded.

Responses and toxicity grades were defined according to WHO criteria (*6*). Patients were classified as no change if the disease remained static for a period of at least 12 weeks. The patients who died during the first 4 weeks without experiencing severe toxicity were classified as early death and were considered ineligible for evaluation for response. Grades of cutaneous and local toxicity were defined according to the WHO criteria reported in table 1.

At least two courses of menogaril were given unless there were clear contraindications. Patients with definite evidence of disease progression after one course were evaluated for response as early progression and did not receive a second cycle.

According to the protocol, treatment could be discontinued after two courses in patients with progressive disease, after three courses in patients with no change, and after six courses in patients with complete response (CR) or partial responses (PR). Response duration was calculated from the start of therapy until disease progression or introduction of new treatment modalities in patients who were responding to treatment. Only the patients for whom an interim blood count was available 2 weeks after treatment were included in hematologic toxicity analyses. Patients who received the drug through a central catheter were not evaluated for local or cutaneous toxicity.

Table 1. Nonhematologic toxicity in 35 patients eligible for evaluation

Toxicity	No. of patients with WHO toxicity grade—		
	1 (mild)	2 (moderate)	3 (severe)
Nausea/vomiting	16	11	0
Alopecia	3	7	11
Local*	7	4	2
Cutaneous†	1	3	2
Cardiac	1	0	0

*Grade 1, phlebitis (P) without pain; grade 2, P with pain; grade 3, P with vesicles or > 35 cm; and grade 4, P with ulceration.

†Grade 1, erythema (E) < 5 cm; grade 2, E > 5 cm; grade 3, inflammatory E or vesicles; and grade 4, E with ulceration.

Table 2. Characteristics of eligible patients

Characteristics	No. of patients*
Eligible patients	37
Median age in yr (range): 60 (40-74)	
WHO performance status	
0-1	27
2	10
Treatment	
Prior hormone therapy	15 (4)
Prior chemotherapy	5 (1)
Prior chemotherapy and hormone therapy	14 (9)
None	3
Dominant site of disease	
Soft tissue	13
Bone	3
Visceral	21

*Parentheses indicate No. of patients who also received radiotherapy.

Results

Between August 1985 and January 1987, 40 patients were entered into this study. Three patients were subsequently defined as not eligible: two had previously received mitoxantrone and one had never started treatment. Table 2 summarizes the characteristics of the remaining 37 eligible patients. The median number of prior cytotoxic drugs was three (range, one to four). The dominant sites of disease in the patients were soft tissue (35%), bone (8%), liver (27%), and lung (30%). A total of 34 patients were eligible for evaluation for response to therapy and toxicity; one for response only; one for toxicity only; and one died of a cause secondary to progressive disease. The median number of cycles administered was two (range, one to nine). Clinical results of treatment according to previous therapy are indicated in table 3.

Among the 15 patients who received prior hormone therapy only, the administration of menogaril produced 4 PRs (response rate, 26.6%; 95% confidence limits, 8%-55%). The dominant sites of disease in these patients were soft tissue (one), lung (two), and liver (one).

Among the 19 patients who had previously received chemotherapy with and without hormone therapy, two were not evaluated because of early death. In one case the early death was due to an acute myocardial infarction that occurred 4 weeks after the first cycle. PRs of 31 and 18 weeks were reported in two patients with soft tissue disease (response rate, 10.5%; 95% confidence limits, 1%-33%). Both patients had already responded to prior chemotherapy.

Table 4 lists the number of patients who were evaluated for leukopenia after the first cycle of menogaril at full and reduced dosages and their median wbc count nadir and range. In patients with no prior treatment or with only prior hormone therapy, the administration of 200 mg of menogaril/m^2 produced grades 2 and 3 leukopenia in 44% and 19% of the patients, respectively. Median time to nadir was day 15 (range, 8-20); median time to recovery was day 26 (range, 15-51). Thrombocytopenia was never reported. In patients pretreated with chemotherapy, the administration of 200 mg of menogaril/m^2 produced grades 2 and 3 leukopenia in 14% and 28% of the patients, respectively. One patient had life-threatening leukocytopenia and thrombocytopenia that occurred 2 weeks after treatment, but the patient recovered within 2 weeks. Another episode of grade 2 thrombocytopenia was associated with grade 3 leukopenia. Grades 2 and 3 leukopenia were reported in 25% and 17% of

Table 3. Response to menogaril

Previous treatment	No. of patients				
	CR	PR	No change	Progressive disease (early disease progression)	Not able to be evaluated
Hormone therapy	0	4 (40 wk; range, 37-45)	4	7 (4 wk)	0
Chemotherapy	0	1 (18 wk)	0	4 (3 wk)	0
Chemotherapy and hormone therapy	0	1 (31 wk)	0	11 (3 wk)	2
None	0	0	1	2	0

Table 4. Leukopenia after the first cycle of menogaril

Previous treatment	Full dosages (200 mg/m^2)			Reduced dosages (160 mg/m^2)		
	No. of patients treated/able to be evaluated	Wbc count nadir $\times 10^3/\mu$L		No. of patients treated/able to be evaluated	Wbc count nadir $\times 10^3/\mu$L	
		Median	Range		Median	Range
None or hormone therapy	16/14	2.5	1.2-4.4	2/2	-	2.3-2.7
Chemotherapy ± hormone therapy	7/6	1.9	0.9-3.9	12/10	2.9	1.3-4.2

the patients, respectively, who had had prior chemotherapy. After the first administration of menogaril at a dose of 160 mg/m^2, grade 1 thrombocytopenia associated with grade 2 leukopenia was reported in one patient.

Among five patients with no prior chemotherapy, or with only prior hormone therapy, and abnormal alkaline phosphatase and alanine aminotransferase values because of liver metastases, the administration of 200 mg of menogaril/m^2 did not produce a more severe leukopenia than that observed in patients with a normal liver function [median wbc count nadir 3.1 $\times 10^3/\mu$L (range, 2.2-3.4)].

The nonhematologic toxicity observed in 35 patients eligible for evaluation is summarized in table 1. Gastrointestinal toxicity was generally confined to the day of administration, starting about 2 hours after the injection. In one responding patient, treatment with menogaril was interrupted after nine cycles (total dose, 1,800 mg of menogaril/m^2) because echocardiography revealed a slight reduction of the movement of the interventricular septum. Phlebitis and erythema along the vein of injection were reported in 34% and 17% of the patients, respectively. With one exception, erythema was associated with phlebitis. Cutaneous and local toxic effects usually appeared during, or soon after, the infusion and lasted for about 2 weeks. The symptoms always disappeared before the subsequent cycle. One patient showed a widespread erythematous rash with asymptomatic tiny spots the week following each drug administration; treatment was never required. The skin eruption was still present when the patient died of tumor progression 6 weeks after the second cycle. Skin biopsies showed a nonspecific inflammatory perivascular exudate with lymphocytic infiltration of the small vessels. Neither phlebitis nor erythema was observed in the only treatment center where the drug was more rapidly administered. The infusion was shortened because someone observed drug precipitates in the infusion flask and in the tubing, and because of the report that local toxicity became dose limiting in the continuous-infusion schedule. The administration of 500 mL in ~10 minutes on 54 occasions to 21 patients did not produce any additional toxicity.

Discussion

Chemotherapy has clearly reached a plateau in the treatment of advanced breast cancer, and therefore new drugs are actively being sought. The overall response rate of 17% in this study does not reach the limit (20% of responses) that is generally considered to be (in most solid tumors) the cutoff point at which a drug may be considered as being active. However, the extent of prior systemic therapy and, to a lesser degree, other characteristics (dominant site of lesions, disease-free interval, etc.) have a definite impact on the rate of response to cytotoxic drugs used for advanced breast cancer (*7,8*). For example, doxorubicin, the most active single agent, has a response rate of 40% in previously untreated patients and 20% in previously treated patients (*7,9*).

In our trial, the patients' characteristics were not particularly favorable or unfavorable. The response rate was 22% (95% confidence interval, 6.4%-48%) in the 18 patients with no prior chemotherapy but dropped to 10% (two of 19 patients) in those with prior chemotherapy.

Our results are consistent with the preliminary findings of two ongoing studies (*10,11*). In a Canadian study, four of 16 patients with no prior chemotherapy responded to menogaril (*11*), while in the study at the Mayo Clinic three of 22 patients with prior first-line chemotherapy (14%; 95% confidence interval, 3%-35%) achieved PR. In the latter study, 10 patients subsequently received treatment with doxorubicin and four objective responses were observed (*10*). Therefore, it is likely that menogaril will prove to be inferior to doxorubicin with regard to antitumor activity. The toxicity pattern of menogaril could, however, be more favorable.

In our study, myelosuppression was predictable and manageable. The incidence and degree of leukopenia were similar in the presence of hepatic dysfunction, which suggests that a reduction of the dosage of menogaril could not be required in patients with liver impairment. This finding agrees with pharmacokinetic data (*12*). Gastrointestinal toxicity and alopecia were milder than generally observed in patients treated with doxorubicin. Menogaril was chosen for clinical evaluation mainly with the hope of developing a less cardiotoxic anthracycline. Although this side effect is difficult to evaluate in early phase II trials, we did not observe any clear-cut cardiotoxic event.

Skin toxicity, mainly phlebitis and erythema, was already observed in phase I trials (*4,5*) and also confirmed in other phase II studies (*10,11,13,14*). This unpleasant toxic effect seems to be related to the infusion duration. This was confirmed in one of our centers, where the drug (diluted in 500 mL of 5% dextrose) was infused in only 10 minutes without cutaneous side effects. The problem of toxic effects of the

skin must definitely be solved before the drug can be considered for further evaluation and possible incorporation in combination chemotherapy.

In summary, our results show that menogaril is an active drug in the treatment of patients with breast cancer who have had no prior chemotherapy. However, its activity seems to be limited in patients already pretreated with cytotoxic drugs.

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Inhibition of Interferon Gamma Production by Benzene and Benzene Metabolites[1,2,3]

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We exposed spleen cells from female Swiss/Webster mice to benzene and benzene metabolites to determine the effects of such exposure on interferon gamma induction by concanavalin A. Exposing the cells to benzene or phenol did not affect interferon gamma production, but exposing them to *p*-benzoquinone, catechol, or hydroquinone significantly inhibited interferon gamma production. Cell viability, as determined by trypan blue viability staining, was not influenced by the chemical treatment. When interferon gamma production was inhibited, the inhibition was dose dependent. The time of optimum production of interferon gamma after exposure to concanavalin A was not affected by treatment of the cells with *p*-benzoquinone. These data indicate the importance of dihydroxy and diketo metabolites as immunotoxic derivatives of benzene. [J Natl Cancer Inst 1988;80:1069-1072]

Benzene has been used extensively in industry as a solvent or a chemical intermediate for the production of pesticides and dyes (*1*). As a result of its antiknock properties, benzene has been added to unleaded gasoline as a replacement for alkyl-lead compounds (*2*). In recent years, benzene has become a ubiquitous environmental pollutant; the common exposure route is the inhalation of automobile exhaust or gasoline fumes. Benzene is a known mutagen and possible carcinogen. Studies in humans and animals have shown that exposure to benzene can cause different forms of blood dyscrasia (*3,4*) and cancer (*5-9*).

Several investigators have demonstrated that benzene metabolism is required for production of toxic effects. Substantial evidence has accrued to suggest that the quinone metabolites of benzene are the true toxic derivatives (*10-12*). These metabolites have been shown to affect a variety of biological processes (*13-16*) including many immunological processes (*17,18*). It has also been determined that exposure to benzene or its metabolites can alter the makeup of lymphocyte subpopulations (*19*), inhibit interleukin-2 (IL-2) synthesis (*17*), depress mitogen-induced blastogenesis of B and T lymphocytes (*18*), and affect maturation of lymphopoietic cells (*20*). However, the full range of the action of benzene and its metabolites on the immune system has not been established.

Interferon gamma (IFN gamma), an important lymphokine, has been shown to be involved in regulation of many aspects of immune responses. IFN gamma has been shown to enhance B-cell maturation (*21*), augment histocompatibility antigen expression (*22, 23*), activate natural killer cells (*24*), and induce differentiation of cell types (*25*). In view of the significant role of IFN gamma in regulation of the immune system, the current study was undertaken to determine if benzene or its metabolites could affect the production of IFN gamma.

Materials and Methods

Materials

Benzene and *p*-benzoquinone were obtained from Fisher Scientific Co.,

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[3]All animals were cared for in a facility accredited by the American Association for Accreditation of Laboratory Animal Care according to National Institutes of Health guidelines under the supervision of a veterinarian.

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