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Clinical Trials Summaries

Negative Phase II Trial of Menogaril in Advanced Squamous, Adeno- and Large Cell Carcinoma of the Lung

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INTRODUCTION

MENOGARIL (NSC 269148, 7-con-*O*-methylnogarol, menogarol) is the most promising of several semisynthetic anthracycline antibiotics derived from nogalamycin [1]. Menogaril and doxorubicin share the tetracyclic, anthraquinone-containing system, but there are several structural differences between the two compounds. The spectrum of antitumor activity of menogaril against experimental murine tumors is broad [1, 2]. The cardiotoxicity of menogaril, evaluated in chronically treated rabbits, has been shown to be less than 1/15th that of doxorubicin [3]. Since menogaril is five to ten times less potent than doxorubicin with regard to antitumor activity, menogaril may have a better therapeutic index than doxorubicin. In a phase I study of menogaril performed by members of the EORTC Early Clinical Trials group a 2-h infusion every 4–5 weeks schedule was explored [4]. Myelosuppression was dose-limiting. Local toxicity consisting of phlebitis and/or erythema was the most common nonhematologic toxic effect.

The present phase II trial was undertaken to determine if the drug could achieve complete or partial responses in non-small cell lung cancer and to further characterize its toxic effects.

MATERIALS AND METHODS

Forty-six patients with histologically documented and surgically incurable squamous cell, adeno- or large cell carcinoma of the lung were entered between May 1985 and September 1986. All patients had locally advanced or metastatic disease with previously unirradiated bi- or unidimensional measurable parameters. No patient was pretreated with chemotherapy.

Menogaril was supplied by Upjohn International Inc. as a sterile freeze-dried preparation. Each 30 ml vial contained 50 mg menogaril, 16.6 mg lactic acid USP and 100 mg mannitol. The vials were reconstituted with 10 ml sterile water for injection and mixed well to yield a clear solution containing 5 mg/ml of menogaril. Good-risk patients defined as patients with a performance score of 0 or 1, no prior extensive radiotherapy and no diffuse bone metastases received a starting dose of 200 mg/m^2 i.v. q 4 weeks. Poor-risk patients defined as patients with a performance status 2 or extensive prior radiotherapy or diffuse bone metastases were treated with a starting

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Table 1. Patient characteristics and response

		NC*	P	ETD	ENTD	Total
Median age in years (range)	61 (36–74)					
Male : female	33 : 11					
Total		15	26	1	2	44
Histology						
Squamous cell		8	10	0	0	18
Adeno		5	10	0	1	16
Large cell		1	6	1	1	9
Other		1	0	0	0	1
Stage						
Locoregional		8	15	0	2	25
Metastatic		7	11	1	0	19
Performance score						
0		2	5	0	0	7
1		11	16	1	0	28
2		2	5	0	2	9

*NC = no change, P = progressive disease, ETD = early toxic death, ENTD = early non-toxic death.

dose of 160 mg/m^2 i.v. q 4 weeks. The drug was administered as an infusion (subdivided into two to three parts) through a large vein over a period of approx. 2 h. Each of the two to three fractions of menogaril was diluted in 150–250 ml of 5% dextrose just before the administration (yielding a final concentration of less than 1 mg per ml). Drug administration was postponed by 1 week if there was no full hematologic recovery at the time of scheduled retreatment. The dosage was adjusted according to the lowest value of the WBCs and platelets measured weekly during the previous course. Response to treatment was first assessed at 4 weeks according to WHO response criteria [5].

RESULTS

The characteristics of the 46 patients entered into the trial are summarized in Table 1. One patient was ineligible because of lack of measurable tumor parameters. One patient was inevaluable due to incomplete documentation. Limited and metastatic disease was defined using the criteria of the V.A. Lung Cancer Group [6]. As stated above no patient had received prior chemotherapy.

No objective tumor responses were observed among the 44 evaluable patients. Fifteen patients achieved disease stabilization for a median of 121 days (51–197+ days). In 26 patients the disease progressed despite the treatment. Two patients died prior to the first response assessment on day 12 and 21 respectively (early non-toxic deaths). A 62-year-old man with a large cell carcinoma metastatic to distant lymph nodes and a performance score of 1 developed 12 days after the first menogaril administration a WBC and platelet nadir of 1400/mm^3 and 30,000/mm^3 respectively and died 2 days later of a septicemia. This patient was considered an early toxic death. The response assessment according to selected prognostic factors is shown in Table 1. The overall median survival was 180 days (12–480 days). Patients with stable disease survived for a median of 180 days (90–390 days), whereas patients with progressive disease had a median survival of 90 days (30–480+).

Myelosuppression was the most significant toxic effect. The median WBC nadir was 2900/mm^3 with a range of 900–12,200/mm^3. Full recovery was seen at a median of 27 days. Only one patient had a leucocyte nadir below 1000/mm^3 and only two patients developed a relevant infection during the period of leucopenia (1 patient with a pneumonia, 1 patient with a septicemia as described above). The median platelet nadir was 250,000 per mm^3 with a range from 30,000 to 489,000/mm^3. Two patients had a drop of their platelet count below 100,000/mm^3. The most frequent non-hematological side effect was local toxicity after the drug administration with 30 of 41 patients (73%) suffering from either cutaneous irritation and/or phlebitis. Three patients suffered from a severe phlebitis. Two patients had a severe skin reaction; in one of these patients the cutaneous toxicity was due to a paravenous injection. Twenty-four of 41 patients (58%) suffered from usually mild nausea and vomiting. Thirteen patients (32%) exhibited hair-loss, which was severe in only one case. One patient developed premature ventricular beats after the administration of menogaril. The patient died from progressive tumor. At the *post mortem* examination no cardiac abnormalities were detected.

DISCUSSION

In this phase II trial menogaril was evaluated in a favorable group of patients with non-small cell lung cancer. All patients were ambulatory and 57% of the patients had locoregional disease. None of the patients had received prior chemotherapy and only two patients had received prior radiotherapy. No objective response was observed among 44 evaluable patients, thus precluding meaningful clinical activity of menogaril in this notoriously chemotherapy-refractory disease.

Menogaril was generally well tolerated. Moderate myelosuppression was observed in the majority of the patients, but 11 patients (25%) experienced no hematological toxicity. Nausea and vomiting were usually mild and occured in less than two-thirds of the patients (58%). Despite the dilution of menogaril to a concentration of 1mg/ml or less, the 2-h infusion and the fractionated application of the drug, 73% of the patients suffered from local toxicity. Clearly this potential for skin and vein irritation might limit the long-term use of menogaril in patients with responsive tumors. Therefore further exploration of the oral route is warranted as one possible way to circumvent this problem [7].

We conclude that menogaril, in the present dose and schedule, is an inactive agent in patients with squamous cell, adeno- and large cell carcinoma of the lung.

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