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Clinical Trials Summaries

Phase II Trial of Menogaril in Advanced Malignant Melanoma. An EORTC Trial

STEIN GUNDERSEN,* SILVIO MONFARDINI,† GEORGETTE RENARD,‡ MARTINE VAN GLABBEKE§ and HERBERT PINEDO‖

**Det Norske Radiumhospital, 0310 Oslo 3, Norway, †Centro Di Riferimento Oncologico, Via Pedemontana, 33081 Aviano, Italy, ‡Institut Jules Bordet, rue Héger-Bordet, 1000 Brussels, Belgium, §EORTC Data Center, 1 rue Héger-Bordet, 1000 Brussels, Belgium and ‖Free University Hospital, De Boelelaan, 1117, NL-1081 HV Amsterdam, The Netherlands*

MENOGARIL (NSC-269148, 7-OMEN, 7-con-*O*-methylnogaril) is a semi-synthetic anthracycline developed by structural modification of the antitumor antibiotic nogalamycin [1]. Screening data showed significant anticancer activity against a number of murine malignancies including i.p. P 388 leukemia and i.p. B 16 melanoma [2]. Menogaril appeared to be active also against the colon 26 and colon 38 tumors, and CD8F1 mammary tumor. Phase I clinical trials were undertaken by the Early Clinical Trials Group using a single dose schedule every 4 weeks. Dose limiting toxicity was leucopenia. Thrombocytopenia was less frequently observed than leucopenia. There was no evidence of cumulative myelosuppression.

The major non-hematologic side-effect was acute skin toxicity, consisting of erythema and/or painful phlebitis at the site of injection. Moderate nausea/vomiting and partial alopecia were registered at doses of 160 mg/m^2 or higher. Hepatic toxicity consisted of an early reversible increase in alkaline phosphatase reported in one patient without known liver metastases. Bradycardia was observed on the electrocardiograms of three patients treated at 200 mg/m^2.

The recommended dose for phase II trials was 160–200 mg/m^2 depending on the status of the patient with respect to prior chemo- and radiotherapy. The present study was done to evaluate whether this new anthracycline showed antitumor activity in patients with malignant melanoma.

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All patients had histologically confirmed progressive malignant melanoma with previously non-irradiated measurable or evaluable lesions. None of the patients had disease amenable to curative surgery while no one received chemotherapy previously.

Eligibility criteria included performance status (WHO) <3, life expectancy ≥3 months, age ≤75 years, white blood cell counts (WBC) ≥4.0 × 10 g/l, platelet counts ≥100 × 10 g/l, serum bilirubin level ≤35 μmol/l and serum creatinine level ≤120 μmol/l. Initial work-up consisted of history and physical examinations, complete blood cell counts, routine chemistry profile and chest X-rays. Blood cell counts were repeated weekly.

In the initial patients Menogaril was given as an i.v. infusion in 5% dextrose divided in three doses each delivered over 30 min up to a total dose of 200 mg/m^2. With this technique, phlebitis, which was occasionally severe, was experienced. When however the total dose was delivered in a volume of 0.5 l, within 10 min this side-effect could be practically eliminated. Dosage adjustments were planned for each course according to WBC and platelet nadirs from the previous course. If treatment was delayed due to myelosuppression drug dosage was reduced to 75% if not indicated by nadir values. The dose was increased by 15% with WBC ≥2.5 and platelets ≥100 × 10 g/l, reduced by 25% with WBC between 1.0 and 1.9 or platelets between 50 and 74.9 × 10 g/l, or 50% for respective values <1.0 and <50 × 10 g/l.

Menogaril was supplied by Upjohn Inter-

Table 1. *Patient characteristics*

Number of evaluable patients	18
Men/women	13-5
Median age in years (range)	50 (29–69)
Median WHO performance score (range)	0 (0–2)
Prior chemotherapy	0
Prior radiotherapy	1
Number of indicator lesions	
Regional nodes	3
Skin	24
Lung metastases	15
Median number of courses	1 (1–12)

national, Inc., in vials containing 50 mg Menogaril as a sterile powder, 16.6 mg lactic acid, USP and 100 mg mannitol. Prior to use, the drug was reconstituted in 10 ml sterile water for each vial and then diluted in 5% dextrose.

The criteria for response were those recommended by UICC.

Of 19 registered patients one was considered ineligible due to prior chemotherapy. The 18 evaluable patients had no previous exposure to radiotherapy, while one patient had received radiotherapy at other sites than indicator lesions. Patient characteristics can be seen from Table 1. Ten patients received one treatment course, five received two courses. The three remaining patients received four, eight and 12 courses. Only one patient had dose reductions due to leucopenia. He has achieved a complete remission of multiple skin metastases after two courses, received eight courses and is still in remission after 1 year. He has been 5 months off treatment. Two patients had stable disease. The remaining 15 patients had progressive disease (five patients after two treatment cycles, 10 patients after one cycle). The median WBC and platelet nadirs were 3.6 × 10 g/l (1.3–6.1) and 191 × 10 g/l (83–362) after the first course. Through all courses the respective values were the same for WBC and 106 × 10 g/l (83–362) for platelets. Phlebitis was observed in nine patients, the severity of which corresponded to WHO grade 1 in one patient, grade 2 in eight patients and grade 3 in one patient. The remaining seven patients received the drug in a 10 min infusion instead of over approx. 1.5 h as originally planned, and experienced no phlebitis.

Nausea grade 1 was seen in three patients while the remaining patients experienced virtually no nausea. One patient had diarrhea grade 1 and two had hair loss grade 1. Oral toxicity was not noted. The most disturbing toxicity was pronounced local phlebitis when infused over a 1.5 h period as stated in the protocol. This was virtually eliminated by reducing the infusion time to 10 min. This has later been confirmed for more than 50 courses delivered to breast cancer patients treated in the Early Clinical Trials Group. No complications have yet occurred due to the short infusion time. Among this group of patients where most had received chemotherapy previously and where more courses were given to each patient, considerably more alopecia and somewhat more pronounced nausea and vomiting was observed as compared to the melanoma study reported here.

It can be concluded that Menogaril has minimal activity in advanced malignant melanoma. The drug appears to be well tolerated but should be infused over a short period of approximately 10 min. Thus the drug appears a candidate in e.g. breast cancer.

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