A phase I clinical and pharmacokinetic study of the oral and the oral/intravenous administration of menogaril

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Summary

Thirty-five patients with advanced refractory cancer were enrolled on this phase I study of menogaril administered orally every 4 weeks at dosages ranging from 85 mg/m² to 625 mg/m². An additional 12 patients received alternating oral and IV doses of menogaril (250 mg/m² IV; 250–500 mg/m² oral) with accompanying blood and urine sampling for pharmacokinetics analysis. Nausea and vomiting were the dose-limiting toxicities at the 625 mg/m² dosage level; vomiting was inadequately relieved by prophylactic antiemetics at this dosage level. Other toxicities included sporadic leukopenia at all dosage levels; at dosages of 500 mg/m² and 625 mg/m², leukopenia < 3000/µl occurred in 7 of 24 patients. Anemia and thrombocytopenia were much less frequent toxicities. Among the patients receiving IV menogaril, peripheral vein phlebitis, leukopenia and anemia were the predominant toxicities. No antitumor responses were observed, yet one patient with non-small cell lung cancer experienced a 30% reduction in metastatic tumor nodules.

For the patients receiving alternating oral and IV menogaril, comparative pharmacokinetic analyses were performed by HPLC. After oral administration, maximum plasma concentrations were achieved in an average of 6 hours; maximum plasma concentrations were less than one-quarter of those achieved after intravenous administration. The harmonic mean (± SD) terminal disposition half-life after oral dosing was 29.3 ± 9.2 hours; mean systemic bioavailability was 33.6 ± 10.5% after oral dosing. Forty-eight hours after an oral dose, mean cumulative urinary excretions of menogaril and the primary metabolite, N-demethylmenogaril, were 4.00 ± 0.96% and 0.44 ± 0.16%, respectively.

Because of the poor tolerance of oral menogaril and minimal evidence of biological activity, this schedule of drug administration is not recommended for phase II evaluation. Based on this and other published studies of oral menogaril, frequent chronic low-intermediate dosages of the drug may be given orally with potentially better tolerance and antitumor activity.

Introduction

The anthracycline anticancer agents have assumed an important role in the systemic management of a wide variety of hematologic and solid malignancies. However, this useful activity comes at a cost in substantial toxicity and the prompt development of drug resistance in the treated tumor. In an effort to exploit the considerable utility of the anthracycline antibiotics, preclinical and clinical evaluations of
other anthracycline agents have continued, seeking to identify those agents with equivalent or greater activity and with less or different toxicities.

Menogaril (7-[R]-O-methylnogaril; NSC-269148) is an anthracycline anticancer agent synthesized from nogalamycin, a fermentation-derived product of *Streptomyces nogalater* [1]. The significant preclinical antitumor activity of nogalamycin was accompanied by severe toxicities in treated animals which precluded this agent’s further clinical development [2]. The derivative agent, menogaril, preserves much of the antitumor activity of the parent compound while sharing few of its toxicities.

Menogaril’s antitumor activity may be mediated through mechanisms which differ from other anthracycline antibiotics. Menogaril accumulates predominantly in the cytoplasm and is cytotoxic at concentrations at which DNA binding and inhibition of DNA and RNA synthesis are minimal [3,4]. Animal toxicology data have been obtained in monkeys, rats, beagles and rabbits and demonstrate that menogaril produces predominantly hematologic toxicity including anemia, leukopenia, lymphocytopenia, and thrombocytopenia [5]. Mild hepatotoxicity, vomiting, alopecia, lethargy, lipemia, weight loss and bloody diarrhea were also observed. Chronic cardiotoxicity studies in rabbits demonstrated that menogaril is 1/15 as cardiotoxic as doxorubicin [6].

In mice inoculated with P388 or L1210 leukemias, orally administered menogaril produced antitumor responses and toxicity equivalent to intraperitoneally administered drug [7]. The aggregate data suggesting an agent with considerable antitumor activity, an acceptable clinical toxicity profile, and a novel route of administration led to the performance of this phase I trial of orally administered menogaril.

Six phase I studies of the intravenous administration of menogaril have been concluded [8-13]. Cumulative maximum tolerated dosages of menogaril for these trials which utilized a variety of administration schedules ranged from 224 mg/m² to 378 mg/m². Leukopenia was dose-limiting, and concentration-dependent venous pain and phlebitis were commonly induced. Nausea, vomiting, alopecia, minor cardiac arrhythmias, fever, anorexia, stomatitis, and fatigue were infrequently observed in these studies.

**Materials and methods**

**Overview**

Eligible patients were enrolled either on a phase I study of the oral administration of menogaril or on a pharmacokinetic study of alternating oral and intravenous menogaril. Blood and urine specimens were collected from those individuals on the pharmacokinetic study for determination of parent drug and metabolite pharmacokinetic behavior.

**Treatment plan**

Eligible patients had histopathological evidence of advanced or metastatic cancer refractory to all known forms of effective therapy, a predicted life expectancy of 12 weeks or more, and a Zubrod performance status of 3 or better. Patients were 18 years of age or greater, had received no prior anticancer therapy for at least 4 weeks, and had recovered from all toxicities of prior therapy. All patients were able to tolerate oral medication. Evidence of organ function consistent with adequate tolerance of menogaril and satisfactory metabolism of the drug was demonstrated for all patients: WBC ≥ 4000/µl; granulocytes ≥ 1500/µl; platelets ≥ 100,000/µl; hemoglobin ≥ 10 gm/dl; serum bilirubin ≤ 2.0 mg/dl; SGOT and alkaline phosphatase ≤ 2 times the upper limit of normal; normal prothrombin time; urea nitrogen ≤ 25 mg/dl; serum creatinine < 1.5 mg/dl; left ventricular ejection fraction ≥ 45% by MUGA scan in all patients treated with doxorubicin at dosages less than 250 mg/m². Patients were ineligible if previously treated with doxorubicin at dosages greater than 250 mg/m², if a myocardial infarction had been suffered within 1 year, or if requiring active therapy for congestive heart failure. All women of child-bearing potential had negative pregnancy tests and were utilizing effective birth control methods. All patients provided written informed consent consis-