Phase I trial of ilmofosine as a 24 hour infusion weekly

M. von Mehren, B.J. Giantonio, C. McAleer, R. Schilder, J. McPhillips, P.J. O'Dwyer
Fox Chase Cancer Center, Philadelphia, PA, USA

Abstract

Ilmofosine, an ether lipid derivative of lysophosphatidylcholine has antineoplastic activity in vitro and in vivo. Maximum efficacy in preclinical models is associated with prolonged exposure to the drug. In a Phase I trial of a weekly 2 hour infusion schedule of ilmofosine, a syndrome of lethargy, diminished performance status, and mild hepatotoxicity was dose-limiting at 550 mg/m². To avoid the higher drug concentrations associated with a brief infusion, a Phase I study of a weekly 24 hour infusional schedule was undertaken in an attempt to maximize dose-intensity. Doses were escalated from 550 to 800 mg/m². Toxicities included nausea, anorexia, fatigue, and minor elevations of liver function tests. The dose limiting toxicity at 800 mg/m² was a syndrome of severe abdominal pain. No neutropenia or thrombocytopenia was observed except in one patient who was found to have a myelodysplastic syndrome, thought not to be related to drug therapy. The more prolonged infusion schedule of ilmofosine did not result in a substantial increase in the tolerable dose.

Introduction

Ilmofosine (BM41.440, 1-hexadecylthio-2-methoxymethyl-rac-glycero-3-phosphocholine) is a thio-ether derivative of lysophosphatidylcholine, an intermediate in membrane phospholipid metabolism. The cytotoxicity of ilmofosine appears to result from its interaction with the plasma membrane: altered permeability and fluidity results in disruption of membrane integrity and function [2]. In addition, inhibition of protein kinase C has been reported [3]. In preclinical studies, ilmofosine was found to have dose-dependent antitumor activity in vitro and in vivo systems. Hanauske et al. demonstrated in vitro inhibition of human explants of non-small cell lung, breast, colorectal, ovarian, renal cell cancer, and melanoma [1]. Prolonged exposure to ilmofosine yielded greater cytotoxicity than brief exposures. Mice bearing xenografts of Lewis lung carcinoma and methylcholanthrene-induced fibrosarcoma demonstrated a dose-dependent inhibition in the growth and metastasis of their tumors [4,5]. Toxicities noted in preclinical studies included lethargy and ptosis at lethal doses, with enteritis, peritonitis, pulmonary edema, and liver and spleen swelling noted at autopsy in mice and rats [6].

The initial Phase I study of ilmofosine administered as a one hour infusion at doses ranging from 25–100 mg was associated with thrombosis, orthostatic hypotension, and mild elevations in transaminases [7]. Studies using oral ilmofosine at doses of 0.5 to 7.0 mg/kg as a single dose in cancer patients revealed dose-limiting toxicities of nausea, vomiting and diarrhea; no renal, hepatic or hematologic toxicities were noted. We performed a Phase I study of ilmofosine as a 2 hour i.v. infusion weekly. The recommended Phase II dose was 550 mg/m²; gastrointestinal toxicity, elevated liver enzymes, and a general decline in functional status were dose limiting at 650 mg/m² [8]. To determine if lower peak levels would modify toxicity and allow the use of higher doses, we piloted the use of a more prolonged infusion schedule.

This Phase I study examined the toxicity and efficacy of ilmofosine in patients with refractory solid tumors given as a 24 hour i.v. infusion weekly for the first four weeks, repeated every six weeks.
We found that the more prolonged infusion resulted in previously unidentified side effects, and that the increase in the dose tolerated was not sufficient to warrant broad-based evaluation of this schedule.

Materials and methods

Patient population

Patients eligible for this study had a histological diagnosis of cancer and had exhausted the standard therapeutic options for their disease. They were over the age of 18 with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and a life expectancy of at least three months. They had an adequate bone marrow (white blood cell ≥ 3500/mm³; absolute neutrophil count ≥ 1500/mm³; hemoglobin > 9.0 gm/dl; platelets ≥ 100,000/mm³), liver (alanine and aspartate transaminases < twice the upper limit of normal; bilirubin < 1.8 mg/dl), and kidney (creatinine < 1.8 mg/dl) function. Patients were excluded if they had a diagnosis of leukemia or multiple myeloma; brain metastases; history of congestive heart failure, pulmonary embolus or deep venous thrombosis, or currently on anticoagulation therapy; active infection or uncontrolled diabetes. Women with child bearing potential were required to have a negative pregnancy test prior to therapy and to use adequate birth control. There was no limit on prior therapy, but patients had to have completed all other cancer therapy more than three weeks before starting ilmofosine (more than six weeks if that therapy included mitomycin C or nitrosoureas), and to have recovered from all toxicities. All patients signed informed consent approved by the Investigational Review Board of Fox Chase Cancer Center.

Drug and dose escalation

Ilmofosine was supplied in ampules containing 250 mg per 10 ml by Boehringer Mannheim Pharmaceuticals Corporation, Rockville, Maryland. Ilmofosine was administered as a 24 hour infusion in 1000 ml D5W via a central venous catheter given weekly for four weeks followed by two weeks off of therapy. Patients were hospitalized for a total of 72 hours during the first dose to monitor for toxicity; during subsequent cycles, patients were hospitalized for their infusion only. Dosage was begun at 550 mg/m² based on the maximum tolerated dose (MTD) of the 2 hour infusion schedule. The dose was increased in successive cohorts of patients until the MTD was reached. Doses were not escalated further in patients who received more than one course. Toxicity was graded using the criteria of the World Health Organization [9]. The MTD was defined as the highest dose that produced reversible toxicity of Grade 2 or less in at least four of six patients.

Patient evaluation

Before treatment, a history and complete physical examination were performed. A complete blood count, prothrombin and partial thromboplastin times, serum electrolytes, uric acid, cholesterol, creatinine, transaminases, as well as urinalysis were obtained before treatment and at least once a week thereafter. Patients were evaluable if they had completed one full cycle of therapy (4 weekly infusions) or developed toxicity that precluded its completion. Tumor response was evaluated if patients had measurable disease defined as a palpable mass with two dimensional measurements, a liver scan defect of at least 5 cm, a radiographic CT lesion of at least 2 cm, x-ray evidence of a two dimensional pulmonary lesion, or hepatomegaly at least 5 cm below the costal margin at the mid clavicular line or xiphoid process on physical exam with biopsy proven cancer. Response criteria were standard [10]. Patients were removed from the study for disease progression or for irreversible toxicity.

Results

Patient characteristics

Fifteen patients were enrolled on study. The patient characteristics are summarized in Table 1. Two thirds of the patients were evaluable for response; all patients were evaluable for toxicity. The major-