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Phase II trial of N-methylformamide in lung cancer

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Introduction

Polar solvents have been investigated for potential anticancer activity because of *in vitro* anticancer effects and, in particular, the property to induce differentiation of malignant cells [1]. N-methylformamide (NMF) is a polar solvent with anticancer activity against human colon cancer xenografts in nude mice [2] and the ability to induce HL 60 promyelocytic leukemia cells to differentiate along the granulocytic pathway [3,4]. Preclinical animal studies and early phase I and II studies [5,6] have identified marked, transient, chemical hepatitis as the dose-limiting toxicity. The presumed novel mechanism of action and non-myelosuppressive toxicity make NMF an attractive antineoplastic agent with the potential to be used in combination therapy.

Methods

The study was approved by the University of Michigan Institutional Review Board, and patients provided their written informed consent prior to treatment. Eligible patients had histologically confirmed, metastatic lung cancer. Previously untreated patients were randomized to treatment with either NMF as a single agent or a cisplatin/plant alkaloid-based combination. At the time of disease progression, patients were offered treatment on the opposite arm of the study. Each patient had at least one measurable lesion and a Karnofsky performance status $\geq$ 50%. Adequate hematologic (WBC $>$ 3,000 cells/mm^3, platelets $>$ 100,000 cells/mm^3), renal (creatine $<$ 2.5 mg%), and hepatic (transaminases $<$ 2$\times$ normal, bilirubin $<$ 2.0 mg%) function were required. Baseline studies included detailed history and physical examination, CBC, differential, biochemistry profile, prothrombin time, partial thromboplastin time, and urinalysis. Liver imaging was performed if the liver enzymes or bilirubin were abnormal at baseline.

The first two patients on the study were treated with NMF at 1,000 mg/m^2 I.V. on 5 consecutive days every 4 weeks. Because of severe, prolonged hepatotoxicity, the dose of NMF was lowered to 800 mg/m^2 I.V. on 5 consecutive days every 4 weeks in subsequent patients.

Dosage adjustments were made on the basis of hepatic toxicity. Subsequent treatments were held until liver enzymes and bilirubin recovered to baseline values. If the bilirubin rose to $>$ 3.0 mg% or the liver enzymes to more than 3 times the upper limits of normal, the subsequent treatment was at 50% dose. Patients experiencing grade 3 or higher nausea and vomiting were treated with a 25% dose reduction at subsequent courses. Patients were considered evaluable if one cycle of treatment and follow-up (4 weeks) was completed.

Results

Table 1 provides the description of the patients entered onto this study and toxicity. No objective responses were seen in 25 patients with non-small cell lung cancer, including 17 who had not received prior chemotherapy and 8 who had crossed over to

Table 1.

Number of patients on study	28	
evaluable for response	26	
evaluable for toxicity	28	
Male:female	26:2	
Karnofsky performance status (median)	80	(50–90)
Age (median)	57	(39–72)
Histology of primary tumor		
Adenocarcinoma	17	
Squamous	4	
Large cell	6	
Small cell	1	
Sites of metastatic disease		
* Lung	11	
* Lymph nodes	8	
* Adrenal	5	
* Liver	1	
(Bone	6)	
(Brain	3)	
(Pericardium	1)	
Toxicity		
Nausea and vomiting		
Grade 0, 1	19	
Grade ≥ 2	11	
Hepatic		
Grade 3	10	

* represents measurable disease sites.

NMF after failing a cisplatin/plant alkaloid-based regimen, and in 1 patient with refractory small cell lung cancer.

Discussion

The absence of objective responses in 25 patients with non-small cell lung cancer, including 17 who had not received prior chemotherapy, excludes (with 95% confidence) response rates greater than 14% and 20%, respectively. We therefore conclude that despite considerable gastrointestinal toxicity, NMF lacks efficacy in non-small cell lung cancer in the dose and schedule used in this trial. Notably, there were 6 objective responses among 12 patients who failed NMF as initial therapy and subsequently crossed over to a cisplatin/plant alkaloid-based combination.

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