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Phase II trial of N-methylformamide in advanced head and neck cancer

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Summary

Eighteen patients with advanced epidermoid carcinoma of the head and neck were entered into a phase II trial of N-Methylformamide (NMF), 800 mg/M^2 IV daily for 5 days every 4 weeks. Seventeen patients had received prior radiation therapy and 11 were previously treated with chemotherapy. No complete or partial responses were observed. The major toxicity was gastrointestinal. Fifty percent of patients experienced nausea and vomiting or reversible hepatotoxicity with greater than a 3-fold elevation of liver enzymes. Mild reversible myelosuppression occurred in 2 patients. NMF in this dose and schedule was not a useful agent to treat recurrent epidermoid carcinoma of the head and neck.

Introduction

N-Methylformamide (NMF) is a metabolite of dimethylformamide (DMF) a widely used industrial polar solvent. NMF was found to be cytotoxic in rodent tumor models [1, 2] and underwent clinical testing at Memorial Sloan Kettering Institute in 1956. Five patients were treated with oral NMF, but treatment was discontinued due to hepatotoxicity [3]. Further study of NMF was abandoned until Dexter *et al.* reported that N-dimethylformamide (DMF)-treated human colon carcinoma cell lines lost their ability to grow in soft agar and were less tumorigenic in athymic mice [4]. This differentiating ability rekindled interest in NMF and prompted testing against the National Cancer Institute human tumor xenograft panel. Antitumor activity was observed against the MX_1 mammary tumor, CX_1 colon tumor, and LX_1 lung xenografts. The drug was also effective against murine sarcoma 180, M5076 ovarian sarcoma, TLXS lymphoma, AKR leukemia, and Ehrich ascites carcinoma and only moderately active against L 1210 and P388 leukemias [5, 6].

Four Phase I clinical studies completed to date recommended doses of 800 mg/M^2/day X5 orally every 2–3 weeks [7], 2000 mg/M^2/week X3 IV [8] and 1,125 mg/M^2/week X6 IV [9], and 1000 mg/M^2/day X5 IV every 3–4 weeks [10]. The dose limiting toxic effects included nausea, vomiting, anorexia, malaise, and liver function abnormalities. This study evaluated the antitumor activity of NMF in head and neck cancer using the phase I 5 day intravenous bolus schedule studied by Spremulli and Coworkers [10].

Methods and materials

Eighteen patients with histologically confirmed epidermoid carcinoma of the head and neck were entered in the study. All patients had measurable disease, a Karnofsky performance score of at least 50%, an expected survival of at least 8 weeks, wbc count > 3500 cells/mm^3, platelet count > 100,000/μl, serum creatinine < 2.5 mg%, serum bilirubin < 2.0 mg and SGOT and SGPT not elevated more than twice normal. A chest roentgeno-

gram, electrocardiogram, alkaline phosphatase, SGOT, SGPT, LDH, bilirubin, total protein, albumin, uric acid, PT, PTT and urinalysis were obtained prior to each cycle. Patients with an unstable cardiac status were excluded because of the risk of myocardial damage reported in pre-clinical screening. The initial dose of NMF was 800 mg/M^2 diluted to a volume of 250 ml D5W in glass bottles administered by peripheral IV infusion over 15 minutes daily for 5 days. Treatment was repeated every 4 weeks. Dose modifications were based on gastrointestinal (GI) toxicity of the preceding cycle. In the absence of toxicity, 2 dose escalations of 100 mg/M^2 each cycle for a maximum of 1000 mg/M^2 $\times$ 5 days were allowed. If liver function tests (LFTs) were abnormal but elevated less than 3 times normal, the same dose of NMF was given. If the LFTs became greater than 3 times normal during the 5 daily treatments, NMF was held until LFTs returned to normal. For Southwest Oncology Group grade 2 GI toxicity (abdominal pain; constipation for 2–4 days; diarrhea producing greater than 4 liquid stools; and more than 5 vomiting episodes in 24 hours) treatment was withheld until toxicity resolved and reinstituted at a 25% dose reduction. Liver function tests were measured daily during treatment, then every two weeks, CBC and platelet counts were performed every two weeks and measurable disease parameters were assessed every 4 weeks. An adequate trial required one cycle and 4 weeks survival. Standard response criteria defined in previous trials were used [11].

Table 1. Patient characteristics

	No. of patients
Total	18
Median age in years (range)	60 (46–69)
Sex	
Male	11
Female	7
Median performance status (range)	70 (60–90)
Prior treatment	
Surgery + RT	6
RT + Chemo	5
Surgery + RT + Chemo	6
No Prior Treatment	1
Primary site	
Oropharynx	4
Skin	1
Oral Cavity	4
Pyriform Sinus	2
Maxilla	1
Hypopharynx	4
Undetermined	1
Larynx	1
Sites of measureable disease	
1°	4
Neck	10
Lung	5
Skin	1
Courses of NMF	
1	13
2	4
3	1

Results

Patient characteristics are shown in Table 1. Of the 18 patients entered on study, 17 had recurrent disease and one was newly diagnosed with advanced, incurable disease. Seven patients had not received prior chemotherapy. Patients at our institution were initially started at an NMF dose of 1000 mg/M^2/day $\times$ 5. Three patients were entered at this dose. In concurrent evaluation of NMF in lung cancer patients at our institution, one patient receiving 1000 mg/M^2/day $\times$ 5 days developed severe hepatotoxicity with a total bilirubin of 4.9 mg/dl (normal range 0.1–0.9 mg/dl), alkaline phosphatase 647 (30–96 IU), SGOT 117 (2–35 IU), SGPT 440 (2–35 IU) and right upper quadrant abdominal pain, nausea, vomiting and anorexia [12]. All subsequent patients entering NMF protocols were started at 800 mg/M^2/day $\times$ 5 days.

Eighteen patients were evaluable for response and toxicity. No complete or partial responses were observed; 12 patients rapidly progressed after only 1 cycle. A total of 24 cycles were administered. Toxicities consisted of grade 1 nausea and vomiting in 3 patients, grade 2 in 2 patients, grade 3 in 4 patients. Elevation of SGOT 3 $\times$ baseline was seen in 4/24 cycles, SGPT 3 $\times$ baseline in 7/24, alkaline phosphatase 3 $\times$ baseline in 3/24. LDH and total bilirubin were not elevated greater than 3 $\times$ base-

Table 2. Toxicity

Dose	No. of pts	No. of cycles	No. of patients Nausea and vomiting Grade 1	Grade 2	Grade 3
600 mg/M^2	1	1	0	0	0
800 mg/M^2	15	17	1	2	4
900 mg/M^2	1	1	1	0	0
1000 mg/M^2	4	5	1	0	0
				Hepatotoxicity LFTs 3 × baseline	
600 mg/M^2	1	1		0	
800 mg/M^2	15	17		10*	
900 mg/M^2	1	1		0	
1000 mg/M^2	4	5		1	

*One patient receiving 800 mg/M^2/day × 5 days had severe hepatotoxicity with LFTs 100 × baseline.

line in any of 24 cycles. One patient had SGOT and SGPT elevation greater than 100 × baseline. This patient was removed from study secondary to hepatotoxicity. The LFTs did return to baseline. Two patients had persistent elevation of SGOT, SGPT and alkaline phosphatase which delayed retreatment. Nine of 18 patients developed nausea and vomiting. Nausea and vomiting was associated with liver enzyme elevation in 6 of 9 patients. Myelosuppression occurred in two patients, nadir WBC count 3,000 and 3,200 and nadir platelet count 62,000 and 35,000. Two patients had dosage escalations, one from 800 mg/M^2/day to 1000 mg/M^2, and the second from 800 mg/M^2/day to 900 mg/M^2/day. One patient had a dosage decrease from 800 mg/M^2/day to 600 mg/M^2/day due to hepatotoxicity.

Discussion

In this phase II trial of NMF for advanced epidermoid carcinoma of the head and neck no clinical responses were observed. This excludes a 20% response rate with 95% confidence. All patients except one had prior treatment that included radiation therapy although forty percent (7/18) of patients had no prior chemotherapy. Rapid progression of disease was seen in 12 patients after one dose of NMF. The major toxicity which was treatment-limiting was hepatotoxicity. We conclude that NMF in the present dose and schedule is not a useful agent for the treatment of epidermoid carcinoma of the head and neck.

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