Investigational New Drugs **11**: 335-336, 1993.

Brief report

A phase II trial of gallium nitrate in advanced previously untreated colorectal cancer

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Key words: colon cancer, advanced, gallium nitrate

Introduction

Gallium nitrate, a heavy metal salt, was chosen for study in advanced colorectal cancer. Gallium nitrate is the anhydrate salt of the naturally occurring heavy metal. Pre-clinical studies showed antitumor activity in a variety of murine tumor cell lines including adenocarcinoma 755 [1]. Clinical activity has been demonstrated in lymphoma [2,3] and small cell lung cancer [4]. Phase I clinical trials in humans suggested a phase II dose schedule of 300 mg/m^2/d for three days every two weeks [5].

Methods

From 1/88 to 1/90 we treated 11 male and 3 female patients with advanced measurable colorectal cancer. No patient had had prior chemotherapy. All patients had pre-therapy computed tomographic (CT) scans, carcinoembryonic antigen (CEA), chest roentgenogram (CXR), and normal renal and hepatic function.

Patients ranged in age from 45–83. Sites of metastases included liver (14), lung (5), pelvis (2), peritoneum (1), and spleen (1).

Patients received gallium nitrate 300 mg/m^2 on day 1, 2, 3. Patients were hydrated with one liter normal saline and given mannitol 25 g prior to each dose and gallium nitrate was infused over 1 hour. Chemotherapy cycles were repeated every 14 days.

Patients were examined prior to each cycle of therapy. Restaging was done after three cycles of therapy unless symptoms or laboratory abnormalities suggested progression. In those instances, reevaluation was performed promptly. Patients having a new lesion or a greater than 25% increase in the sum of perpendicular diameters of existing lesions were considered to have progressive disease. A partial response was defined as a 50% reduction in the sum of perpendicular diameters of any lesion, with no increase in any lesion and no new lesions. Stable disease was defined as neither progression nor response.

Results

Fourteen patients were entered on study. Six patients received three, seven patients received two, and one patient received one cycle of therapy. One patient who received three cycles of therapy had stable disease but refused further therapy. All other patients had progressive disease documented by follow-up CT scans.

Toxicities and complications

Toxicities are summarized in Table 1. No patient had severe or life-threatening toxicity. Asymptomatic hypocalcemia was common, but responded to oral calcium supplements. One patient required intravenous magnesium and potassium supplementation. No patient developed renal insufficiency. Elevations of LDH above 5× normal were

Table 1. Toxicity of Gallium Nitrate

	(Common Toxicity Criteria)			
Grade	1	2	3	4
Anemia	1	4		
Nausea	2	6	1	
Vomiting		2	1	
Elevated transaminases	4			
Elevated alkalinephos	2	3		
Elevated LDH			9	
Pulmonary		3		
Neuro	1			
Fever		1		
Hypocalcemia	4	4		
Hypomagnesemia			1	
Hypokalemia	2			
Metallic taste	2			

common, but levels dropped within 1–2 weeks of discontinuation of gallium nitrate therapy.

Discussion

None of 14 patients treated with gallium nitrate at the dose and schedule employed in this trial had an objective response to therapy. It is, therefore, unlikely that gallium nitrate at this dose and schedule would produce an objective response rate greater than or equal to 20% if additional patients were treated. Further investigation of this drug in this setting is unwarranted.

Notably, seven patients subsequently received fluorouracil containing chemotherapy and three had a partial response suggesting that gallium nitrate did not influence the ability to give subsequent therapy. Therefore, testing of new agents in previously untreated patients is still warranted and seems not to be detrimental to patients with advanced malignancies such as colorectal cancer, in whom the survival benefit from standard chemotherapy is marginal.

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