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Phase II evaluation of MGBG in non-small cell carcinoma of the lung

A Southwest Oncology Group Study

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Summary

One hundred and eight patients with non-small cell lung cancer were treated in a Phase II trial with MGBG at a dose of 600 mg/m^2 i.v. weekly. Partial responses were noted in 3/43 patients with adenocarcinoma and 1/40 with squamous cell carcinoma. No responses were noted in 24 patients with large cell carcinoma. Overall, the drug was reasonably well-tolerated. At this dosage and schedule, MGBG has no substantial antitumor activity for patients with non-small cell lung cancer.

Introduction

Methyl-glyoxal-bis-guanylhydrazone (MGBG) was first described by Freedlander in 1958 as having *in vitro* antitumor activity (1). The mechanism of action of the drug is thought to be related to inhibition of the enzyme S-adenosyl methionine (SAM) decarboxylase which catalyzes synthesis of spermidine (2). MGBG in concentrations as low as 0.5 micrograms/ml is a potent inhibitor of spermidine biosynthesis (3, 4, 5). At concentrations of 2 to 8 μM (0.6 – 2.4 micrograms/ml), MGBG appears to act selectively on polymine synthesis. At concentrations as high as 100 μM (30 micrograms/ml) or more, the drug has other direct toxic effects, including inhibition of protein synthesis (4) and complete inhibition of mitochondrial respiration (5). There is evidence to suggest that spermidine is of importance in the initiation of DNA synthesis and that MGBG-mediated depression of DNA synthesis is associated with spermidine depletion (6 – 8).

Responses to MGBG in clinical trials were first noted in acute myelocytic leukemia (9 – 11). Other clinical studies have noted responses in carcinoma of the breast, renal carcinoma, lymphoma, colon carcinoma, pancreatic carcinoma, and carcinoma of the esophagus and bladder (12 – 18). Since there are no known single agents with high order of activity in non-small carcinoma of the lung, the Southwest Oncology (SWOG) conducted a phase II trial of MGBG in this disease entity.

Materials and methods

From twenty member institutions of the Southwest Oncology Group, 108 patients were entered into a study of the efficacy of MGBG in extensive non-small cell carcinoma of the lung. Extensive disease is defined as measurable disease outside of one hemithorax. Of these 108 patients, two were ineligible because of poor performance status (both

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patients had a performance status of 4). Of the 106 remaining patients, two were judged inevaluable because of insufficient data, whereas 15 were considered evaluable for toxicity, but not for response. Of these 15 partially evaluable cases, 9 incurred an early death (within two weeks of study entry), three refused further therapy before three drug doses were administered, one was lost to follow-up after one drug course, one had an inadequate trial because of toxicity, and one progressed after two drug courses rather than the outlined three courses.

Of the 106 eligible cases, 43 (41%) had squamous cell carcinoma, 51 (48%) had adenocarcinoma, and 12 (11%) had large cell anaplastic carcinoma by diagnosis of the institutional pathologist. Males comprised 77% of the patient population. All had measurable disease and a performance status of at least 2 (50% or greater Karnofsky rating). Each patient had a WBC count greater than 3,000/mm^3, platelets greater than 100,000/mm^3, BUN less than 20 mg%, creatinine less than 1.2 mg%, bilirubin less than 2 mg%, and no clinical or chemical evidence of biliary obstruction. A majority (55%) of eligible patients had received no prior chemotherapy.

An initial dose of MGBG of 600 mg/m^2 was given intravenously in D_5W or normal saline over no less than 30 min into a freely running I.V. line. Drug dosages were governed by hematologic toxicity. MGBG was given weekly, providing the WBC count was greater than 3,000/mm^3 and the platelet count was greater than 100,000/mm^3. An adequate trial for therapy consisted of three courses of treatment. The administration of MGBG was held if the WBC count dropped into the range of 2,000 – 2,999/mm^3 or if the platelets fell between 75,000 – 99,999/m^3. Upon recovery, the same dosage was resumed. If the WBC count fell below 2,000/m^3 and/or the platelets below 75,000/m^3, MGBG was not administered until counts recovered into the pre-treatment range. At this point, the dosage was decreased by 100 mg/m^2. For patients who had received prior chemotherapy or radiotherapy, four weeks were required to have elapsed since that therapy.

Gastrointestinal and neuromuscular toxicity also determined therapy. No course of MGBG was given until stomatitis had resolved from the previous course of therapy. After recovery, the next dose of MGBG was decreased by 100 mg/m^2 for severe stomatitis. Patients with mild to moderate diarrhea and/or nausea and vomiting were managed symptomatically. Patients with moderately severe diarrhea or nausea and vomiting (grade 3) had the drug withheld until symptoms abated and then received a 200 mg/m^2 dose reduction. Patients with mild or transient paresthesias received the same dose of MGBG or 100 mg/m^2 reduction in dosage if the paresthesia was severe or continual. Patients with any muscle weakness or pain had CPK, aldolase, and, when feasible, EMG studies performed. MGBG administration was withheld until symptoms of weakness or pain subsided. When symptoms had completely abated, reinstitution of the drug was begun at a 200 mg/m^2 reduction.

Therapeutic responses were defined as follows:

complete remission (CR) – the disappearance of all evidence of disease for greater than one month;

partial remission (PR) – a greater than 50% decrease in the sum of the products of the perpendicular diameters of all measured lesions with no simultaneous increase in the size of any lesion or the appearance of new lesions for at least four weeks;

stable disease – objective tumor regression not qualifying for partial remission but lasting at least four weeks, or a steady state not qualifying for increasing disease of at least eight weeks duration;

increasing disease – unequivocal increase of at least 25% in the size of any measured lesions or the appearance of any new lesion.

Results

Adverse effects

The toxic effects of MGBG in this study confirmed previous reports using this drug (9 – 11, 19). Specifically, the main toxic effects consisted mostly of weakness (33 patients of whom 11 had severe toxi-

Table 1. Type and degree of toxicity

	MGBG				
	None	Mild	Mod.	Sev.	Fatal
Granulocytopenia	104	1	1		
Thrombocytopenia (platelet)	103		2	1	
Anemia	99	1	5	1	
Leukopenia (WBC)	102	2	1	1	
Peripheral neuropathy	73	7	15	11	
Dizziness/hot flashes	102	1	3		
Diarrhea	95	8	2	1	
Weight loss	91	7	6	2	
Nausea/vomiting/anorexia	67	14	12	14	
GI (other)	105		1		
Allergy/rash/epidermitis	102	2	2		
Cardiac (hypotension)	105	1			
Cardiac (other)	104		1	1	
Hematuria	105	1			
Mucositis/ulcers/stomatitis	93	5	5	3	
Venous sclerosis/phlebitis	105	1			
Other	105		1		

Table 2. Responses according to cell type

Cell type	CR	PR	Stable	NR/INC	Unknown
Squamous cell					
Prior XRT					
No	0	1	9	8	3
Yes	0	0	11	11	0
Prior Chemo					
No	0	0	12	12	1
Yes	0	1	8	7	2
Large cell					
Prior XRT					
No	0	0	2	3	1
Yes	0	0	1	4	1
Prior Chemo					
No	0	0	2	3	0
Yes	0	0	1	4	2
Adenocarcinoma					
Prior XRT					
No	0	2	7	12	4
Yes	0	1	9	12	4
Prior Chemo					
No	0	2	13	9	5
Yes	0	1	3	15	3

city) and nausea and vomiting (40 patients of whom 14 had severe symptoms). Other toxic effects included weight loss (15 patients), mucositis and stomatitis (13 patients), and diarrhea (11 patients). (The complete list of adverse effects can be seen in Table 1.)

Response

There were no complete remissions and four partial remissions in the group. Table 2 shows that three patients of the four responders were adenocarcinomas (3/43 = 7%) and the remaining responder was squamous cell carcinoma (1/40 = 2.5%) for an overall response rate of 4.5% (4/93) in the evaluable group. The comparison among the three cell types did not show any significant difference ($p = 0.393$). There were, in addition, thirty-nine patients (41.9%) with stable disease in the study. The patients who received no prior chemotherapy had median survivals of twenty-two weeks while those patients who were previously treated had median survivals of ten weeks ($p = 0.113$). There was no difference in survival between male and female patients.

Discussion

Eighty-nine patients with non-small cell carcinoma of the lung were adequately treated with MGBG. The drug was generally well-tolerated. Weakness, nausea and vomiting, weight loss, and mucositis and stomatitis were the most often observed side effects.

There were four partial remissions reported (4/93 = 4.3%). Three of the four responders had histologically proven adenocarcinoma with the remaining responder having squamous cell carcinoma. Thirty-nine patients exhibited stable disease (39/93 = 41.9%). Two of the four responders had received no prior chemotherapy. It is, therefore, our conclusion that at this specific dose level and frequency of administration, MGBG did not show adequate activity in any histologic cell type of the non-small cell variety. Furthermore, we do not feel that further investigation of the drug as a single agent in non-small cell carcinoma of the lung is warranted.

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