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Phase II trial of gallium nitrate, amonafide and teniposide in metastatic non-small cell lung cancer

An Eastern Cooperative Oncology Group study (E2588)

Alex Y. Chang[1], Z. Nora Tu[2], Julia L. Smith[3], Philip Bonomi[4], Thomas J. Smith[5], Peter H. Wiernik[6] and Ronald Blum[7]

[1]*University of Rochester/Genesee Hospital, Rochester, NY;* [2]*M.D. Anderson Cancer Center, Houston, TX;* [3]*University of Rochester Cancer Center, Rochester, NY;* [4]*Rush-Presbyterian/St. Luke's Medical Center, Chicago, IL;* [5]*H. Lee Moffit Cancer Center, Tampa, FL;* [6]*Albert Einstein Cancer Center, Bronx, NY;* [7]*New York University Medical Center, New York, NY, USA*

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Summary

Fifty-five patients with metastatic non-small cell lung cancer (NSCLC) were entered into this phase II randomized study for evaluating three new agents: gallium nitrate, amonafide and teniposide. The patients had to have ECOG performance status 0 or 1, no prior chemotherapy, and adequate hematological, hepatic and renal functions. Forty-seven patients were eligible and evaluable. Fourteen were randomized to receive gallium nitrate, 18 to amonafide and 15 to teniposide. Seventy-four percent of eligible patients were male. The majority of patients (89%) had an ECOG performance status 1. ECOG grade 4 toxicity occurred twice in patients on gallium nitrate, seven times on amonafide and 18 times on teniposide. The cause of death was attributed to amonafide in one patient (from sepsis) and to teniposide in two patients (due to infection and leukopenia). There was no objective response in all the patients entered. The overall survival times ranged from 2 weeks to 156 weeks with a median of 23 weeks. There were no survival differences among the three treatment arms. We conclude that gallium nitrate, amonafide and teniposide are inactive in metastatic NSCLC and do not warrant any further testing in this disease.

Introduction

Lung cancer is the leading cause of cancer death in both men and women in the United States. It is also a major healthcare problem in the entire world. It is estimated that about 180,000 new cases of lung cancer will occur in 1994 [1]. About 75–80% of them are non-small cell lung cancer (NSCLC). Since only a small proportion of the patients will be cured by surgery, the majority of the patients with NSCLC will have recurrent or metastatic disease and require systemic treatment. In the past decade, chemotherapy has not been shown consistently to prolong the survival in this group of patients although modest benefit was noted by meta-analysis [2–4]. Hence, the search for more active agents with novel mechanisms of actions has been the major thrust of the Lung Committee in the Eastern Cooperative Oncology Group (ECOG) in the last decade. Here, we report the results of an ECOG study of three new agents, gallium nitrate, teniposide and amonafide.

Gallium nitrate (NSC 15200) is a heavy metal

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salt. It partially inhibits DNA and RNA-dependent polymerase [5]. However the exact mechanism of cytotoxicity of gallium nitrate is unknown. It is thought to involve the metal's ability to concentrate in the malignant tumors rather than normal tissues or serum. It was hypothesized that gallium binds to transferrin to form a complex which in turn binds to the tumor cell surface and exerts a cytotoxic effect [6,7]. Amonafide (NSC 308847), a derivative of 3-nitro-1,8 naphthalic acid, is a DNA intercalating agent with the ability of causing single strand DNA breakage [8]. Teniposide (NSC 122819) is a new derivative of etoposide which is one of the active agents against NSCLC. Teniposide exerts its cytotoxicity by blocking topoisomerase II activity. All these three new agents have been shown to be active in pre-clinical *in vitro* testing and in animal tumor models before entering the clinical studies [8–11]. Earlier trials with gallium nitrate showed clinical activity in lymphoma, small cell lung cancer and bladder cancer [12]. Preliminary data suggested teniposide may be an active agent in the treatment of non-small cell lung cancer [13].

Materials and methods

Patient selection

The criteria for patients to enter into this study were histologically confirmed NSCLC, measurable metastatic or recurrent disease, ECOG performance status 0 or 1, and no prior chemotherapy. The patients were also required to have adequate bone marrow (WBC $\geq$ 4,000/mm^3 and platelet $\geq$ 100,000/mm^3), hepatic (bilirubin $\leq$ 1.5 mg/dl and SGOT $\leq 2\times$ normal) and renal functions (BUN $\leq$ 25 mg/dl, creatinine $\leq$ 1.5 mg/dl and creatinine clearance $\geq$ 60 ml/min). The patients were ineligible if they had received radiation treatment within two weeks prior to starting protocol treatments, had received prior radiation treatment to the only disease site, had uncontrolled diabetes mellitus or cardiac disease.

Treatment plan

Patients were initially randomized to gallium nitrate and amonafide. If there were no responses in the initial 16 patients on either arm, then that arm was to be substituted with teniposide. Treatment was assigned randomly to patients using permuted block, stratified by weight loss greater/equal versus less than 5% in the previous 6 months. The treatment dose and schedule of three agents were as follows:

- gallium nitrate 300 mg/m^2 in one liter of D5W or normal saline IV infusion over 24 hours daily for 7 days every four weeks;
- amonafide 300 mg/m^2 in 50–100 cc normal saline IV infusion over 60 minutes daily for 5 days every 3 weeks;
- teniposide, 160 mg/m^2 in 250 cc normal saline IV infusion over 60 minutes days 1, 3, and 5 every 3 weeks.

Standard ECOG criteria for solid tumor response and toxicity were used in the evaluation of all cases [14]. In brief, complete response (CR) indicated disappearance of all clinically detectable disease for at least four weeks without the appearance of any new lesion. Partial response (PR) was defined as a reduction equal to or greater than 50% of the size of the indicator lesions for at least 4 weeks. Progressive disease (PD) is an increase > 25% of the lesion present at the start of therapy or after a response or appearance of new metastatic lesions. Deterioration of performance status by more than one level related to malignancy or loss of weight > 10% of pre-treatment level, and a need for palliative radiation therapy during the treatment course were all considered progressive disease. Stable disease (SD) was defined as a response that can not fit into the above three definitions.

Patients with a CR, PR, or SD were to continue treatment until PD unless the toxicities were prohibitive.

Statistical methods

Two-stage accrual design was used in this protocol as follows: each arm would initially accrue 16 patients and then closed until response data were available. If at least 1 response was observed, the

Table 1. Distribution of patient characteristics by treatment

Patient characteristics	Treatment GN		AM		TE		Total	
	N	%	N	%	N	%	N	%
Sex								
Male	8	57	15	83	12	80	35	74
Female	6	43	3	17	3	20	12	26
Age								
Median	56		63.5		60		61	
Range	42–69		51–79		37–74		37–79	
Initial performance status								
Full active	0	0	2	11	2	13	4	9
Ambulatory	14	100	16	89	13	87	42	91
Weight loss in previous six months								
None	3	21	6	33	5	33	14	30
< 5%	3	21	6	33	5	33	14	30
5–10%	1	7	3	17	4	27	8	17
> 10%	7	50	3	17	1	7	11	23
Histology								
Squamous	4	29	9	50	4	27	17	36
Adenocarcinoma	7	50	6	33	4	27	17	36
Large cell anaplastic	2	14	1	6	3	20	6	13
Other	1	7	2	11	4	27	7	15

GN: gallium nitrate; AM: amonafide; TE: teniposide.

arm would reopen and would accrue an additional 28 patients. This was to ensure at least 40 eligible patients for analysis. Based on this two-stage design, there is at most a 5% chance of stopping early (0/14 response) if the true underlying response rate is 20%. The survival curves were estimated using the method of Kaplan and Meier [15].

Results

A total of 55 patients were entered into the study. Three were cancelled before treatment started due to one of the following: a need for radiation therapy, development of brain metastases, and severe bone pain with deterioration of performance status. There were four ineligible patients (two with active cardiac disease on study; one had no pre-treatment creatinine clearance; and one had no distant metastases). One other patient was lost for follow-up. All of these eight patients were excluded from analysis.

Table 1 summarizes the pre-treatment characteristics of the remaining 47 eligible and analyzable patients. Sixty-four percent had previous surgery while thirty-four percent had previous radiation therapy. Patients in three treatment arms were comparable.

Toxicity and response

Table 2 depicts all the incidences of grade 3 or greater toxicities according to the treatment arm. Gallium nitrate caused only two incidences of grade 4 toxicities, while amonafide had 7 and teniposide had 18. Most common toxicity was myelosuppression. Leucopenia and infection were the cause of death in two patients treated with teniposide and one patient treated with amonafide. In addition, grade 3 or greater hepatic toxicity occurred in three patients treated with teniposide. There were no incidences of renal, cardiac or allergic toxicities. There were no objective responses in any of the patients evaluated. There were 6 patients with stable disease and 33 patients had progression

Table 2. Incidence of toxicity

	GN			AM			TE		
Grade	3	4	5	3	4	5	3	4	5
WBC	–	–	–	5	3	–	6	5	2
Granulocytes	–	–	–	2	2	–	4	6	2
Platelets	–	–	–	–	1	–	1	3	2
Hemoglobin	3	–	–	1	–	–	3	2	–
Infection	–	–	–	–	–	1	2	1	2
Nausea	–	–	–	1	–	–	–	–	–
Vomiting	–	–	–	–	1	–	1	–	–
Diarrhea	–	–	–	–	–	–	1	–	–
Stomatitis	1	–	–	–	–	–	1	–	–
Hepatic	–	–	–	1	–	–	1	1	1
Pulmonary	–	1	–	–	–	–	2	–	–

GN: gallium nitrate; AM: amonafide; TE: teniposide.

of disease. The remaining 8 patients were unevaluable and all were counted as disease progression.

Survival

The overall survival time was calculated from the date of randomization to the date of death or the date of last known to be alive. The overall median survival time was 23 weeks with a range of 2 to 156 weeks. The median survival time for gallium nitrate, amonafide and teniposide were 24.4 weeks, 22.7 weeks and 13.3 weeks, respectively. There were no differences in the survival among the three treatment arms.

Discussion

Gallium nitrate, amonafide and teniposide in the dose and schedule tested in our study has a manageable toxicity profile except for myelosuppression. Teniposide caused higher incidence of grade 4 and 5 myelosuppression/infection in this group of patients. We have used a high dose of teniposide in this study. This may be the reason for increased myelosuppression.

The main purpose of this study is to evaluate anti-tumor efficacy and toxicity of gallium nitrate, amonafide and teniposide in patients with metastatic NSCLC. Our results suggest that none of these agents would have a 20% response rate (with 90% statistical power) and thus none of them were active against metastatic NSCLC in the dose and schedule studied. We cannot substantiate the early report on teniposide [13]. It is possible that we might underdose amonafide in some patients who were slow acetylators because Ratain *et al.* have recently recommended 375 mg/m^2 amonafide for this group of patients [16]. We also cannot rule out the possibility that we may give gallium nitrate at a higher dose and observe a better response rate, since most patients tolerated gallium nitrate very well.

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Address for offprints: A.Y. Chang, Medical Oncolog Division, The Genesee Hospital, 224 Alexander St., Rochester, NY 14607, USA