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A phase II trial of gallium nitrate (NSC #15200) in advanced or recurrent squamous cell carcinoma of the cervix

A Gynecologic Oncology Group study

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Abstract

Twenty-four evaluable patients with advanced, persistent or recurrent squamous cell carcinoma of the cervix were treated with 750 mg/m² of gallium nitrate (NCS # 15200) every three weeks. No patient had prior cytotoxic chemotherapy. Two patients had a partial response (8.3%), ten patients had stable disease (41.7%), and twelve (50%) had increasing disease. The 95% upper confidence bound for response is 24.0%. The major toxicities were nausea, vomiting and anemia. Gallium nitrate has minimal activity in patients with previously untreated squamous cell carcinoma of the cervix.

Introduction

Gallium is a naturally occurring heavy metal. Gallium nitrate is produced by dissolving the gallium metal or its oxide in concentrated nitric acid [1]. The activity of gallium nitrate is believed to be derived from its ability to concentrate in tumor tissue to a greater extent than normal tissue [2]. The mechanism of uptake is unknown. *In vitro* studies have indicated that most gallium is bound to be B-globulin transferrin in the serum. Tumor cells may then accumulate the gallium probably by means of an active transport process. Once in the cell, gallium may work by enzyme inhibition of various DNA polymerases [3].

Preclinical evaluation demonstrated activity in several animal tumor systems including Walker 256 carcinosarcoma, fibrosarcoma M-89, adenocarcinoma 755, reticulum cell carcinoma A-RCS, lymphosarcoma P 1798 and osteosarcoma 124F [1]. Phase I trials suggested a phase II dosage and schedule of 750 mg/m² repeated every three weeks [4]. The Pharmaceutical Resources Branch of the National Cancer Institute provided the gallium nitrate (NSC #15200) as an investigational anticancer drug. The Gynecologic Oncology Group (GOG)

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University of Alabama at Birmingham (CA 12484), The Oregon Health Sciences Center University*, University of California Medical Center at Los Angeles (CA 13630), University of North Carolina School of Medicine (CA 23073), Bowman Gray School of Medicine of Wake Forest University (CA 21946), The Albany Medical College of Union University (CA 27469), University of Pittsburgh School of Medicine*, Eastern Virginia Medical School (CA 40296), State University of New York at Stony Brook* and Pennsylvania Hospital*.
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selected this agent for study in women with advanced or recurrent squamous cell carcinoma of the cervix. The study was completed between January and December of 1988.

Materials and methods

Eligibility required that patients have histologically confirmed advanced, persistent, or recurrent squamous cell carcinoma of the cervix with documented disease progression after local therapy. All patients must have measurable disease (defined as lesions measurable in at least two dimensions by physical examination), no prior therapy with cytotoxic agents, a GOG performance status of 0, 1 or 2 (Karnofsky 50–100), adequate hematologic, renal, hepatic function and informed consent. The starting dose and schedule of gallium nitrate was 750 mg/m^2 every three weeks as a 30–60 minute infusion. Dose escalations were not allowed. Patients were encouraged to drink or be hydrated with at least three liters of fluid the day prior to treatment. An additional 500 cc's of normal saline was infused in the two hours prior to administration of gallium nitrate. Hydration of three liters of fluid orally or intravenously was encouraged during the first 24 hours after therapy. Gallium nitrate was held if pretreatment WBC or platelet count was less than 3,000/μl or 100,000/μl respectively. For patients whose WBC was between 3,000 to 4,000/μl and whose platelets were above 100,000/μl, had a dose level decrease to 600 mg/m^2. Patients with Grade 3 or 4 hematologic toxicity but whose WBC was greater than 4,000/μl and platelets greater than 100,000/μl prior to their next course, also had a dose decrease to 600 mg/m^2. If the creatinine rose to 2 mg% or greater, the drug was withheld until the creatinine decreased to less than or equal to 2 mg%, and the dose was decreased to 600 mg/m^2 on the next course.

Prior to therapy, all patients had history and physical examination, tumor measurements, performance – status assessment, CBC and platelet count, laboratory profile including liver and renal function test, electrocardiogram, and chest X-ray. Patients with measurable disease demonstrable only on computerized tomographic, sonic or radionuclide scan had an initial study and repeat studies at six week intervals, while those with palpable lesions were assessed every three weeks. An adequate trial was defined as patients receiving one course of treatment and living at least three weeks. All patients remained on study until there was evidence of disease progression. Response, performance status and grades of toxicity were defined according to standard previously described GOG criteria [5].

Results

Patient characteristics and response are shown in Table 1. Twenty-six patients were entered into this trial. One patient was ineligible due to the wrong primary, and one inevaluable as she was never treated. The median number of courses given was 2.5 with a range of 1–5. Five patients received only one course. Four patients had rapid progression of their disease after one course and one patient refused further therapy.

Two patients were partial responders (8.3%) and response lasted for four months. The first response occurred in a 66 year-old woman with central cervical recurrence who had greater than 50% shrinkage after two courses of treatment. She ultimately died from widespread abdominal carcinomatosis after four courses of therapy. The second patient, a 38 year-old, had 50% decrease in the size of pulmonary metastasis after one course and died from progressive pulmonary disease after four courses. Ten patients (41.7%) had a stable disease with four months median duration. The remaining 12 patients had increasing disease.

The major toxicity was nausea and vomiting which was mild in two patients, moderate in five and severe in one. Three patients had moderate anemia and one Grade 3 anemia. No myelosuppression or grade 4 toxicity occurred (Table 2).

Conclusion

Gallium nitrate is an interesting drug with very little myelosuppression, which has minimal activity using the present dose schedule in previously untreat-

Table 1. Patient characteristics and response

Characteristic/Response	No.	%
Patients entered	26	
Wrong primary	1	
Never treated	1	
Evaluable	24	(100)
Age median/range	49.5 (28–82)	
GOG performance status		
0	6	(25.0)
1	8	(33.3)
2	10	(41.7)
Prior treatment		
Surgery	16	(66.7)
Radiation	23	(95.8)
# of courses of gallium nitrate (median range)	2.5	(1–5)
Response		
Complete (CR)	0	– –
Partial (PR)	2	(8.3)
Stable	10	(41.7)
Increasing disease	12	(50.0)
Progression-Free Interval-Median	1.8 months	
Survival-Median	3.7 months	

Table 2. Adverse effects

	Grade					
Adverse effects	0	1	2	3	4	Total
Leukopenia	24	0	0	0	0	24
Thrombocytopenia	24	0	0	0	0	24
GI	16	2	5	1	0	24
Anemia	20	0	3	1	0	24
Renal	18	5	1	0	0	24
Weight loss	23	0	0	1	0	24

ed patients with advanced, persistent or recurrent squamous cell carcinoma of the cervix. Based upon the initial response rate, future trials are not recommended with gallium nitrate in patients with squamous cell carcinoma of the cervix.

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