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Phase II evaluation of gallium nitrate by continuous infusion in breast cancer

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Summary

We evaluated the role of gallium nitrate infusion in the treatment of metastatic breast cancer. Gallium nitrate was administered at 300 mg/m^2/day for 7 days every 3 weeks by continuous infusion concomitantly with oral calcium supplement of 500 mg twice daily and oral hydration. Fifteen patients with refractory metastatic breast cancer received such treatment for a total of 30 courses. Median age was 51, and median performance status (Zubrod scale) was 1. These patients had minimal prior chemotherapy (median 1 regimen). All patients were evaluable for toxicity and 14 for response. Nine patients had one to two metastatic sites, five patients had three to four sites. No major objective response was seen, but one patient had a minor response (10 weeks), and another showed no change in disease (16 weeks). Diverse low-grade toxicities were observed, including nausea and vomiting in 11 patients, anorexia in 11, diarrhea in eight, stomatitis in five, dysgeusia in six, musculoskeletal pain in five, skin rash in seven, partially reversible tinnitis and/or mild hearing loss in four and sensory neuropathy in two. A consistent drop in hemoglobin (median of 3.2 g/dL per patient) necessitated blood transfusion in seven patients. There was no granulocytopenia or thrombocytopenia; however, significant lymphopenia was noted. Reversible, moderate nephrotoxicity occurred in two patients. The hypocalcemic effect was consistent, with a median drop in serum calcium of 1.25 mg/dL per course. There was no hepatic toxicity. While no single toxicity was severe, overall toxicity adversely influenced treatment tolerance. Gallium nitrate by continuous infusion, as given in this study, has no activity in metastatic breast cancer.

Introduction

Gallium nitrate was introduced into clinical trials after the demonstration of its greater antitumor activity in mice compared to the other members of the Group IIIa metals [1]. Early clinical trials utilizing brief intravenous infusion schedules [2–4] revealed that nephrotoxicity was dose-limiting. The resurgence of interest in gallium nitrate followed the introduction of the continuous infusion schedule by Warrell *et al.* [5]. This method of administration decreased the incidence and severity of nephrotoxicity and resulted in a higher dose-intenstiy drug delivery, compared to intravenous bolus schedules. Moreover, activity was observed in resistant lymphoma and transitional cell carcinoma of the urinary bladder [5–7]. Gallium nitrate had a potent hypocalcemic effect when given by continuous infusion [8,9], being a helpful agent in the management of hypercalcemia, a common complication of recurrent breast cancer. In heavily pretreated breast cancer patients, the brief intravenous schedule failed to show activity [10]. In this study, gallium nitrate by continuous infusion was evaluated in patients with minimal prior therapy.

Table 1. Patient characteristics

Characteristics	Number (range)
Patients registered	15
Evaluable for toxicity	15
Evaluable for response	14
Median age in years	51 (33–72)
Median performance status (Zubrod)	1 (0–2)
Median prior chemotherapy regimens	1 (1–2)
Prior hormonal treatment	7
Prior radiotherapy	11
Dominant metastatic site	
visceral	8
bone	4
soft tissue	2
Number of metastatic sites	
≤ 2	9
> 2	5
Estrogen receptor	
positive	4
negative	9
unknown	1
Median number of gallium nitrate courses	2 (1–4)

Patients and methods

From January to October 1987, fifteen patients with breast cancer were registered in the study. The patient characteristics are outlined in Table 1. A maximum of two prior chemotherapy regimens was allowed, with a performance status of ≤ 2 (Zubrod scale). Eligible patients were required to have adequate renal (creatinine $\leq$ 1.4 mg/dL), hepatic (bilirubin $<$ 1.5 mg/dL), and bone marrow function (peripheral granulocyte count $\geq$ 1500/dL and platelet count $>$ 100,000/dL). Measurable or evaluable disease was a prerequisite. No other concomitant anticancer therapy or prior cis-platinum chemotherapy was allowed. Participating patients were asked to express their understanding of the investigational aspect of the trial by signing a consent form that was approved by the Internal Review Board of the Institution.

Gallium nitrate (NSC #15200) was supplied by the NCI as 20 ml vials (25 mg/mL). Each mL also contained 28.75 mg trisodium citrate dihydrate and sodium hydroxide to adjust to pH 6.0–7.0. Therapy was administered on an out-patient basis by small volume (60 mL) pump. The starting dose was 300 mg/m^2/24 hrs/day for 7 days every 3 weeks. No prophylactic antiemetics were given. Patients were instructed to maintain a record of oral fluid intake greater than 2 L per day. In the event of suboptimal oral hydration due to gastrointestinal toxicity, intravenous hydration was initiated. Concurrent administration of aminoglycosides or any other potentially nephrotoxic agents was avoided. Because of the anticipated hypocalcemic effect, non-hypercalcemic patients were maintained on oral calcium supplement (Os-Cal 500 [Marion Laboratories] 1 tablet orally twice daily for 7 days) with the start of the infusion.

Baseline hemogram, urinalysis, serum chemistry profile (SMA-12), electrolytes, calcium, magnesium, phosphorus, and 24-hour urine collection for creatinine clearance and protein were performed initially and studies repeated prior to each course. During therapy, patients were monitored twice weekly during the first two weeks, then weekly with serum calcium, phosphorus, and magnesium in addition to weekly hemogram, BUN, and creatinine studies.

Subsequent courses were administered pending recovery of non-hematologic toxicities to grade $\leq$ 1 (modified WHO toxicity grading classification, Table 2). All patients completed a 7-day infusion course and were considered to have received an adequate treatment.

Results

A total of 30 courses of gallium nitrate infusion was given to 15 patients. All courses and patients were evaluable for toxicity, while 14 patients were evaluable for response (non-evaluable disease on retrospective assessment in one patient). Two patients received four courses, nine received two courses, and four were given one course. No major objective response was observed. A minor response ($>$ 25% but $<$ 50% decrease in soft tissue disease) was seen

Table 2. Modified WHO toxicity classification

Toxic effect	Grade 1	Grade II	Grade III
Granulocytes 1000/cmm	1.5–1.9	1.0–1.4	0.5–0.9
Platelets 1000/cmm	75–99	50–74	25–49
Nausea and vomiting	Nausea only	Transient vomiting	Vomiting requiring therapy
* Anorexia	With weight loss ≤ 2 Kg/course	With weight loss > 2 Kg/course	–
Diarrhea	Transient, < 2 days	Tolerable, but > 2 days	Intolerable, requiring therapy
Stomatitis	Erythemia, soreness without ulcers	Ulcers, can eat	Ulcers, can not eat
* Fatigue	Mild, fully ambulatory	Moderate, in bed or chair < 50% of time	Severe, in bed or chair > 50% of time
Dermatitis	Local erythemia, mild or transient rash	Dry desquamation, vesiculation, pruritis, diffuse erythema	Ulcerative, moist desquamation
Nephrotoxicity			
BUN	21–40	41–60	≥ 61
Creatinine	1.25–2.5 × N	2.6–5 × N	5–10 × N

* These toxic effects were not included in the WHO classification.

in one patient for 10 weeks. No change in disease on therapy was noted in another patient (visceral and soft tissue components) for 16 weeks.

The toxicity profile is summarized in Table 3. Although gastrointestinal toxicities were frequent, they were generally mild. Fatigue was a prominent feature and lasted for 1–3 weeks after completion of the infusion. Pruritic, fine, scaly, localized desquamation was observed in four patients, while in three it was diffuse. This pattern of skin toxicity was more prominent in previously irradiated regions. Five febrile episodes were noted during the study period, but no infectious etiology could be documented. A mild-to-moderate hearing loss (affecting 1000 to 8000-Hz frequencies) was documented in two patients. Weight loss was a prominent finding that was generally associated with anorexia. The median weight loss was 4.1 Kg. Only two patients had evidence of weight gain, which could be attributed to fluid retention. Five patients had grade I nephrotoxicity that was manifest by transient elevation in BUN level. However, two patients had reversible grade II nephrotoxicity. Anemia, with a median drop in hemoglobin of 3.2 g/dL/patient (range, 1.7–7.3), necessitated blood transfusion in seven patients. This was also associated with changes in hemoglobin indices (Table 4). No effect on the neutrophil or platelet count was observed (Table 5). However, lymphopenia was a prominent component. The lymphocyte count reached a median nadir of 394 cells/μL (range, 0–1846) per course from a median pretreatment value of 1415 cells/μL (range, 352–2548) ($P < .001$). In nine courses, a biphasic dip in lymphocyte count was evident around the end of the first and third weeks. Moreover, lymphopenia appeared to be a cumulative effect. Such observations were limited by the study requirement of only one hemogram per week and the fact that only two courses were given to the majority (nine patients). The hypocalcemic effect of gallium nitrate infusion was observed in all patients showing cumulative nadirs on repeated infusion. Serum calcium level dropped from a median of 9.6 mg/dL (range, 8.7–11.2) to

Table 3. Percent of patients exhibiting toxicity

Toxic effect	Percentage of patients
Nausea and vomiting	73
grade I	46
grade II–III	27
Anorexia	73
grade I	20
grade II	53
Diarrhea	53
grade I	7
grade II	46
Stomatitis	33
Dysgeusia	40
Fatigue	73
grade I	20
grade II–III	53
Musculoskeletal pain	33
Dermatitis	47
Fever	33
Tinnitis	20
Mild hearing loss	13
Sensory neuropathy	13
Weight loss ≥ 2 kg	87
Nephrotoxicity	47
grade I	33
grade II	14
Anemia (> 1.5 g/dL decrease in hemoglobin)	100
Granulocytopenia	0
Thrombrocytopenia	0
Hypocalcemia (≤ 8.5 mg/dL)	87
Hypophosphatemia (< 2.5 g/dL)	80
Hypomagnesemia (< 1.8 mg/dL)	53

a median of 7.9 mg/dL (range, 5.4–8.8) per course. Hypocalcemia was not symptomatic. In eight courses, oral calcium supplement was not given as recommended in this study (in three courses due to hypercalcemia). There was no noticeable difference in the degree of hypocalcemia with or without the calcium supplement. Hypomagnesemia was not a prominent toxicity. While none of the toxicities were severe, the overall toxicity adversely affected patient tolerance. In four patients there was a 1–2 week delay in starting a subsequent course of therapy until subsidence of toxicity.

Table 4. Change of hemoglobin and red blood cell indices per patient during Ga $(NO_3)_3$ administration.

	Median pretreatment value (range)	Median lowest value (range)
Hemoglobin, g/dL	13.5 (10.1–14.7)	9.1 (6.8–12.4)
Hematocrit, %	41.0 (30.4–44.9)	29.5 (20.7–38.7)
Mean corpuscular volume, fl	92 (82–103)	83 (72–93)
Mean corpuscular hemoglobin, pg	30.9 (27.2–38.8)	27.8 (22.1–30.7)
Mean corpuscular hemoglobin concentration, g/dL	33.0 (31.8–34.4)	33.1 (29.9–34.0)

Table 5. Hematological changes per course during Ga $(NO_3)_3$ administration

	Pretreatment (range)	Nadir (range)	Time to Nadir (Days)
* Leukocytes	6.8 (4.1–9.2)	5.7 (3.8–15.9)	13
Granulocytes	4.2 (2.5–8.0)	3.9 (2.8–13.4)	8
Lymphocytes	1.4 (0.4–2.5)	0.3 (0.0–1.8)	13
Platelets	343 (186–786)	302 (145–593)	8

* Values are expressed as cells × $10^3/\mu L$.

Discussion

This study failed to demonstrate clinical antitumor activity of gallium nitrate infusion at the given dose schedule in metastatic breast cancer (the possibility of observing 20% response rate at a 5% rejection error). Accordingly, additional studies at the same dose and schedule are not indicated in breast cancer. Despite the lack of significant antitumor activity, the hypocalcemic effect was felt to be quite consistent and of potential value in the treatment of hypercalcemia related to malignancies, as has been demonstrated by other studies [8,9]. At the current

dose schedule, however, the overall toxicity profile limited the patients' tolerance and a lower dose schedule or a different route of administration [11] could be more appropriate.

The incidence of gastrointestinal toxicity was higher than other studies using similar dose schedules [5,12–15]. Fatigue and weight loss had not been emphasized previously, and could be secondary to other toxic effects. The magnitude of decrease in hemoglobin was more prominent, in this study, compared to that in other published data [3–5]. A similar finding was reported recently by Scher *et al.* [15] in patients with prostatic cancer. Though no effect on platelet count was noted in this study, a thrombocytopenic effect was observed in other studies using intravenous bolus schedules [3,6]. These observations suggest that gallium nitrate may be of potential value in the treatment of polycythemia vera. The potential therapeutic benefit may not only be achieved by interfering with hemoglobin synthesis but also by the possible antiproliferative effect on the erythroid neoplastic progenitors where such effects have been observed *in vitro* in Friend erythroleukemia by Chitamber *et al.* [16]. Likewise, the activity of the drug in lymphoma and the significant lymphopenic effect demonstrated in this study that has not been outlined in previous studies [2–7,10–15,17,18] indicates that another clinical trial of the drug in chronic lymphocytic leukemia is warranted.

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