Treatment of Patients with Advanced Malignant Lymphoma Using Gallium Nitrate Administered as a Seven-Day Continuous Infusion

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Previous trials of gallium nitrate (NSC-15200) showed that bolus administration produced dose-limiting nephrotoxicity without substantial antitumor activity. As an effort to increase the therapeutic index of this compound and to establish a satisfactory out-patient schedule, the authors evaluated the effects of gallium nitrate administered as a continuous infusion in patients with advanced malignant lymphoma. In an initial Phase I trial, four dose levels which ranged from 200 to 400 mg/m^2/day in 27 patients were studied. Nausea which impaired oral hydration was found to be dose-limiting. A dose of 300 mg/m^2/day was chosen for extended Phase II evaluation and 37 additional patients were entered into the study at that dose level. Overall, 16 of 47 patients (34%) who had bi-dimensionally measurable parameters of disease achieved major antitumor responses (six of 15 with diffuse "histiocytic" lymphoma, five of ten with diffuse poorly-differentiated lymphocytic lymphoma, two of five with nodular poorly-differentiated lymphocytic lymphoma, and three of 17 with Hodgkin's disease). The median duration of response was 2.5 months. Only 8% of patients who received 300 mg/m^2/day developed an increase in serum creatinine concentration >1.1 mg/dl over baseline values. Hypocalcemia occurred in two-thirds of patients. Other toxic effects, including paresthesiae, diarrhea, and hearing loss, were noted in <5% of patients. There was minimal myelosuppression. The authors conclude that gallium nitrate administered as a continuous infusion for seven days at 300 mg/m^2/day is well-tolerated and effective treatment for patients with advanced malignant lymphoma. Outpatient administration using portable infusion pumps is safe and practical. Further evaluation of the drug administered as a constant infusion is indicated in patients with other neoplastic diseases.

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GALLIUM is a metal which belongs to the Group IIIA elements of the periodic table. The antitumor activity of Group IIIA metals was examined by Hart *et al.*[1,2] Various nonradioactive salts of gallium and indium injected intraperitoneally (IP) were found to be cytotoxic against ascitic Walker 256 carcinoma; however, only gallium was active after IP injection when the tumor was implanted subcutaneously.[1]

Several clinical Phase I studies of gallium nitrate have been reported.[3–6] Nephrotoxicity is dose-limiting when the drug is administered as a brief intravenous infusion.[4] Single doses of 750 mg/m^2 [4] or three consecutive daily doses of 300 mg/m^2 [3] administered every 2–3 weeks are tolerated by most patients. Clinical evaluation of gallium nitrate is incomplete. However, preliminary results using intermittent dose schedules have failed to show significant activity in patients with sarcomas of bone and soft-tissue[7] or breast cancer.[8] While isolated responses have been reported in patients with malignant lymphoma,[3,5] these responses have generally been short-lived. No disease-oriented study has yet been reported in lymphoma.

In an attempt to improve the therapeutic index for this compound, we evaluated the effects of gallium nitrate given as a continuous infusion for seven days in patients with advanced malignant lymphoma.

Patients and Methods

Patients with Hodgkin's disease, non-Hodgkin's lymphoma, or cutaneous T-cell lymphoma (mycosis fungoides) who had failed conventional therapy were entered into this study. The treatment protocol required

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histologic confirmation of disease, performance status ≥50 (Karnofsky), total serum bilirubin ≤2.0 mg/dl, serum creatinine ≤1.3 mg/dl, and creatinine clearance ≥70 ml/min. Patients had not received chemotherapy or radiation within three weeks preceeding entry (six weeks for any nitrosourea). No lower limit for hematologic counts was specified. Patients admitted to the dose-finding phase of this study (*i.e.*, the first 27 individuals) were not required to have measurable disease. All other patients had bi-dimensionally measurable parameters of disease.

The pretreatment evaluation included: complete history and physical examination; hemoglobin, leukocyte, and platelet count; a 24 hour urine collection for creatine clearance; serum electrolytes, serum creatinine, 12 channel biochemical screening profile, blood urea nitrogen; and chest roentgenogram. During the initial infusion, patients were monitored with daily measurements of serum creatinine. In the second phase of the study, total serum calcium and magnesium were measured before starting therapy and every three days during the infusion. Body weight, fluid intake, and urinary output were recorded daily. The daily urinary volume was kept ≥2000 ml relying chiefly on oral hydration, using supplemental intravenous fluids where necessary. Patients were reexamined 7–10 days after each infusion and the serum creatinine and creatinine clearance were checked. Patients who were clinically improved after one infusion were eligible for further treatment; those patients who showed no response were given other forms of therapy. All patients gave written informed consent. The study was approved in advance by this Center's Institutional Review Board.

Response Criteria

A complete response was defined as the disappearance of all evidence of disease and normalization of all biochemical parameters for greater than four weeks. In addition, a complete response required restaging which included as a minimum a bone-marrow biopsy and lymphangiography or a computed tomographic scan of the abdomen. A partial response was defined as >50% decrease in the sum of the products of the longest perpendicular diameters of all measurable lesions for at least four weeks. Tumor regressions of <50% or less than four weeks duration were recorded as failures. The duration of response was defined from the date a >50% response was recorded to the date of disease progression. Patients were considered adequately treated and evaluable for response after they received one infusion for seven days.

Method of Administration

The first two infusions of gallium nitrate were administered strictly on an inpatient basis in order to observe for untoward toxicity and to insure adequate hydration. The prescribed dose of gallium nitrate was diluted in 1000 ml of 5% dextrose solution and was infused over a 24 hour period. Infusions were generally administered into a peripheral vein; infusion pumps and central venous access lines were not required. In order to permit an assessment of dose-related cumulative toxicity, dose escalation was not allowed in the same individual.

Responding patients were re-admitted to the hospital within 16–21 days following their first infusion and were given the subsequent infusion into a peripheral vein using portable infusion pumps (Cor-Med Inc., Middleport, NY). Thereafter, infusions were only administered on an out-patient basis using the infusion pumps and relying upon oral hydration. Subsequent infusions were administered every 3–5 weeks. The treatment interval depended in part upon clinical discretion as to patient tolerance, availability of the infusion apparatus, and the duration of the clinical response. The treatment interval was gradually lengthened to a maximum of five weeks for individuals responding for longer than three months.

TABLE 1. Characteristics of Patient Population Treated with Gallium Nitrate

Median age, yrs (range)	42 (17–70)
Median Karnofsky performance status (range)	60 (50–80)
Median number of prior chemotherapy regimens (range)*	3 (1–8)
Median number of prior chemotherapeutic drugs (range)*	9 (4–15)
Histologic subtypes of lymphoma	No. of patients
Hodgkin's disease	23
Diffuse histiocytic (DHL)	19
Diffuse poorly-differentiated lymphocytic (DPDL)	13
Nodular poorly-differentiated lymphocytic (NPDL)	6
Cutaneous T-cell (mycosis fungoides)	3
Major sites of extranodal involvement*	
Bone marrow	20
Lung/pleura	29/6
Liver	4

* Data exclude patients with cutaneous T-cell lymphoma.

Results

A total of 64 patients were treated. The characteristics of this patient population are presented in Table 1. All of these patients had received extensive prior chemotherapy. (A "regimen" was defined as one drug used alone, *i.e.*, an experimental agent, or several drugs used in combination [such as MOPP: mechlorethamine, vincristine, procarbazine, prednisone] for at least four weeks.) Eighty percent of patients had also received radiation; 70% had already failed one or more investigational agents. All but three patients had Stage IV disease (Ann Arbor classification); 60% had one or more major

TABLE 2. Renal Toxicity from Varying Doses of Gallium Nitrate (Phase I Study)

Dose level*	No. of patients	No. of infusions	Median peak Serum creatinine, mg/dl (range)	Median Δ Serum creatinine, mg/dl (range)
200	6	12	1.1 (0.7–1.4)	+0.2 (0 to +0.3)
250	4	9	0.9 (0.7–1.1)	+0.1 (−0.1 to +0.1)
300	7	16	0.8 (0.6–1.6)	+0.1 (−0.1 to +1.0)
400	10	17	1.3 (0.6–8.1)	+0.5 (+0.1 to +6.8)

* Dosage in mg/m^2/day, given as continuous IV infusion for seven days.

organs involved with disease (Table 1). Other-extranodal sites included: skin in seven patients; cortical bone in six; bowel in six; central nervous system in four; stomach in two; pericardium and testis in one patient each.

Dose-Finding Analysis

Twenty-seven patients were entered into the first phase of this study and four dose levels were examined. The incidence of renal toxicity increased with escalations in dose. Table 2 shows the relation between the daily dose level and resulting peak levels in serum creatinine concentration. At the 300 mg/m^2 level, only one of seven patients developed a peak serum creatinine ≥1.5 mg/dl whereas three of ten patients exceeded that value at the 400 mg/m^2 level. (Other aspects of the renal damage are discussed in the Toxicity section.) At the 400 mg/m^2 level, four of ten patients experienced mild nausea which significantly impaired oral fluid intake; this effect had not been seen at lower dose levels. Since we sought to establish a satisfactory outpatient regimen which avoided the use of parenteral hydration, we established a daily dose of 300 mg/sq m for Phase II evaluation.

Therapeutic Effects

Therapeutic responses in 47 patients with bi-dimensionally measurable parameters of disease are shown in Table 3. In the dose-finding phase of this study, we observed objective responses at all four dose levels. Therefore, patients at all dose levels in both phases of this study have been combined for the analysis of response. Overall, 34% of patients with measurable disease had major objective responses. Two of these responses in patients with advanced diffuse histiocytic lymphoma were judged to be complete after restaging evaluation; these responses persisted for durations of 10 and 14+ months, respectively. The remaining responses were partial. The median duration of response for all patients was 2.5 months, ranging from 1 to 14+ months. The response rate in patients with Hodgkin's disease was lower than that for patients with non-Hodgkin's lymphoma (18% *versus* 43%). Objective responses were associated with symptomatic improvement and an increase in performance status. The earliest signs of clinical response were usually not evident before the final 1–2 days of the infusion and were not uncommonly delayed for 7–10 days following its completion.

TABLE 3. Therapeutic Responses in Patients with Relapsed Malignant Lymphoma Treated with Gallium Nitrate Infusions*

Histologic types	No. of patients responding	No. of patients evaluable	Response rate	Response duration (mos)
Hodgkin's	3	17	18%	1.5, 2, 5.5
DHL	6	15	40%	1, 1.5, 2, 2.5, 9+, 10, 14+
DPDL	5	10	50%	1.5, 2, 4, 9.5, 14+
NPDL	2	5	40%	2, 7
Total	16	47	34%	Median = 2.5 mos

* Data are for patients with bi-dimensionally measurable parameters of disease.

In the dose-finding study, ten patients did not have clearly measurable disease parameters. Five of these patients (three of four with HD, one of three with DPDL, one of one with NPDL, 0 of two with DHL) were considered to have experienced sufficient clinical improvement to warrant additional treatment. None of three patients with cutaneous T-cell lymphoma responded. Five patients could not be evaluated for therapeutic response. Infusions were terminated prior to day 7 in two patients who developed early signs of renal insufficiency. Three other patients who showed early evidence of response could not be continued on the study; one developed *Listeria* meningitis, one received large doses of dexamethasone for presumed central nervous system involvement with lymphoma, and one patient expired from *Pneumocystis carinii* pneumonia.

All but one patient with Hodgkin's disease or non-Hodgkin's lymphoma underwent whole-body scanning with gallium-67 (^{67}Ga) citrate prior to entry into the study. Although 95% of those studies revealed increased isotopic accumulation at known tumor sites, only 34% of the patients responded. Imaging in three patients failed to show uptake of ^{67}Ga in any areas known to be involved with lymphoma; one of those patients subsequently showed a partial therapeutic response to the gallium nitrate infusion. Thus, it would appear that results of ^{67}Ga scanning have no predictive value for response to gallium nitrate infusions.

Toxicity

In general, this therapy was very well tolerated. Renal insufficiency was the most important toxic effect. Table 4 shows the change in serum creatinine concentration from baseline to peak values for all patients in the Phase

II study who received 300 mg/m^2/day. Only three of those patients (8%) experienced a rise in serum creatinine ≥1.1 mg/dl at any point during the study. Renal insufficiency was reversible in all instances. Two patients required short-term hemodialysis before kidney function recovered. One of those individuals has received seven additional infusions as an outpatient without deterioration in his renal function. Renal toxicity occurred in three patients who received gentamicin concurrently with the gallium nitrate infusion. We found no evidence of cumulative renal toxicity in patients who received continued treatment for periods up to 14+ months.

Hypocalcemia occurred in two-thirds of patients who received this therapy (Table 4). This effect usually occurred within 3–4 days of starting the infusion and occasionally persisted for several weeks. Most patients were asymptomatic but several individuals complained of muscle cramps and one patient developed mild tetany (positive Chvostek's sign). Both oral and parenteral calcium supplements were administered to these patients. Hypomagnesemia was somewhat less prominent and occurred in ten of 29 patients who entered the Phase II study with normal serum concentrations. A mild hyperchloremic (respiratory) alkalosis was also noted in several patients who had no obvious predisposing condition, *e.g.*, pulmonary lymphoma, fever, etc. The alkalosis corrected following cessation of the infusion.

The extent of drug-induced myelosuppression was somewhat difficult to assess since all patients had received extensive prior therapy and many had varying degrees of myelophthisis or splenomegaly. The changes in hemoglobin concentration during this trial are shown in Table 4. Several patients required blood transfusion for a hypochromic microcytic anemia; both the serum iron and total iron-binding capacity were reduced in those patients. Leukopenia and thrombocytopenia were evaluated in patients who entered this trial with relatively normal hematologic counts, *i.e.*, total leukocyte count ≥3500/mm^3, platelet count ≥120,000/mm^3. Only three of these patients developed a leukocyte count <2500/mm^3 and only one patient developed a platelet count < 50,000/mm^3 at any point during the study.

Nine patients experienced pulmonary complications during this trial with the development of fever, pleural effusions, and interstitial lung infiltrates. Infectious organisms were identified in only three instances (*Pneumocystis carinii* in two, *Bacteroides fragilis* in one). With one exception, these episodes resolved after the use of a variety of empiric antibiotic therapies; two of these patients who were retreated did not experience recurrence of the syndrome. Several other patients developed worsening of their pleural effusions before showing a therapeutic response. Although the requirement for hydration in this study was not excessive, several patients (especially elderly individuals and those who were hypoproteinemic) developed weight gain and peripheral edema during the infusions which necessitated the use of diuretics.

TABLE 4. Toxic Effects of Gallium Nitrate Infusions

Hematologic toxicity	Median	Range
Δ Hemoglobin concentration (g/dl)‡	−1.8	(+1.3 to −5.3)
Leukocyte nadir (1000 cells/mm^3)§	6.0	(1.8 to 15.7)
Platelet nadir (1000 cells/mm^3)§	243	(18 to 688)
+Δ Serum Creatinine Concentration (mg/dl)*	No. of Patients	Percent
<0.4	27	73%
0.5 to 1.0	7	19%
≥1.1	3	8%
−Δ Total Serum Calcium Concentration (mEq/l)†		
<1.0	11	31%
1.1 to 2.4	13	38%
≥2.5	11	31%
Pulmonary complications‡	9	14%
Nausea‡	4	6%
Paresthesia‡	3	5%
Diarrhea‡	3	5%
Decreased auditory acuity‡	2	3%

* Data include all patients in Phase II study (n = 37).
† Data from Phase II study only; values not determined on two patients (n = 35).
‡ Data include all patients in both phases of study (n = 64).
§ Data include all patients entered into both phases of the study with previously "normal" blood counts (n = 39).

Other toxic effects were mild. At the recommended dose (300 mg/m^2/day), no patient experienced nausea or vomiting. Three patients complained of paresthesia in their hands; each had received extensive prior therapy with vinca alkaloids. Three patients experienced mild-to-moderate diarrhea which persisted for 3–5 days after completing the infusion. Two patients developed a mild hearing loss for high frequency sounds which was documented by audiometry.

Discussion

We found that seven-day infusions of gallium nitrate were well-tolerated and effective for the treatment of patients with relapsed lymphoma. The response rate in non-Hodgkin's lymphoma compares favorably with other drugs of proven efficacy for the treatment of this disease, including doxorubicin[12] and bleomycin.[13] The absence of nausea or myelosuppression were particularly important for these patients who had received extensive prior radiation and chemotherapy. Furthermore, outpatient drug administration at the recommended dose (300 mg/m^2/day × seven days) using portable pumps was safe for patients with normal renal function who could rely solely on oral hydration. Because of our desire to establish a satisfactory outpatient schedule, we found that nausea was dose-limiting in this trial. Undoubtedly, higher total daily doses of gallium nitrate (*i.e.* >400 mg/

m^2/day) could be administered with the use of vigorous IV hydration.[4]

Following IV injection, gallium nitrate is almost entirely excreted into the urine.[4,5,9] The terminal plasma half-life is approximately 25 hours but this value is highly dependent upon renal function. During the initial clinical evaluation of gallium nitrate at this center,[5] three patients were treated with the drug administered as a continuous infusion. At a constant daily dose of 200 mg/sq m/day, mean plasma concentrations ranging from 0.9 to 1.9 μg/ml were maintained during the steady state. Conversely, in three patients who received bolus IV injections at doses of 500 or 700 mg/m^2, plasma gallium concentrations were <2.0 μg/ml after 24 hours.[5]

The mechanism whereby gallium exerts its cytotoxic effect is unkown. Limited data[14,15] suggest that gallium impairs Ca++- or Mg++-dependent processes which are critical in rapidly proliferating cells.[16] Following IV injection, gallium is rapidly bound to plasma proteins, principally transferrin.[17] Larson *et al*[10] have shown that transferrin can mediate the entry of ^{67}Ga into tumor cells. The exact nature of the transferrin mediation is unclear and its relevance has been questioned.[17,18] However, several human tumor cell lines express receptors for transferrin[19,20] and the injection of cytotoxic drugs complexed with transferrin has been proposed as a means of "targeting" chemotherapy to tumor tissues.[21]

Nephrotoxicity is the most serious toxic reaction associated with the use of gallium nitrate. Three of the five patients who developed a serum creatinine concentration ≥4.0 mg/dl had received comcomittent treatment with gentamicin. For that reason, we recommend that concurrent use of aminoglycoside antibiotics with gallium nitrate be strictly avoided. The renal lesion is associated with deposition of a gallium–calcium–phosphate complex in the renal tubules.[22] Krakoff *et al*.[4] have shown that maintenance of a high urinary flow minimizes the renal injury by decreasing urinary gallium concentrations; however, the renal clearance of the element is not increased by vigorous hydration. At a daily dose of 300 mg/m^2, we found that maintenance of a urine output ≥2000 ml/24 hrs protected against renal damage.

The high incidence of pulmonary complications in our patients is unusual. Nine of the 64 individuals developed a syndrome characterized by fever, dyspnea, interstitial pulmonary infiltrates, and pleural effusions. In preclinical toxicologic studies, only rodents developed pneumonitis following lethal injections of gallium nitrate.[2] Pulmonary lesions were not evident in other species[23] nor has pulmonary toxicity been reported in other clinical studies. There is no evidence that gallium induces direct injury to lung parenchyma; however, gallium is known to accumulate in pulmonary macrophages.[25] Conceivably, functional impairment of those macrophages would be particularly immunosuppressive and could result in an increased susceptibility to pulmonary infections.

Unlike cisplatin which frequently causes hypomagnesemia,[24] hypocalcemia was an exceptionally prominent reaction to gallium nitrate; hypomagnesemia occurred much less commonly. Preliminary data obtained from patients undergoing careful calcium balance studies do not confirm excessive urinary calcium loss as a mechanism for the observed hypocalcemia.[26] Since gallium-67 can accumulate in crystals of hydroxyapatite,[27] hypocalcemia could result from a decreased rate of calcium resorption from bone. This mechanism may indicate a therapeutic role for gallium nitrate in cancer-related hypercalcemia.

Our results indicate that seven-day infusions of gallium nitrate are safe and effective therapy for patients with advanced malignant lymphoma despite heavy prior treatment. Since the suggested dose for intermittent bolus injections is 700–900 mg/m^2 given every 2–3 weeks,[3,4,6] prolonged infusion (300 mg/m^2/day × 7, 2100 mg/m^2 total dose every 21 days) achieves at least a two-fold increase in the amount of drug which can be safely administered. Additional research should elucidate the mechanism(s) of drug cytotoxicity and incorporation into tumor cells. Gallium nitrate is a unique agent whose toxic effects do not overlap those associated with other drugs commonly used for the treatment of malignant lymphoma. Further investigation of the drug alone and in combination is clearly warranted.

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