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ORIGINAL ARTICLE

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A pharmacokinetic and phase II study of gallium nitrate in patients with non-small cell lung cancer

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Abstract This study investigated the pharmacokinetics and activity of gallium nitrate in non-small cell lung cancer when 700 mg/m^2 was given as a 30-min infusion with prehydration every 2 weeks. Gallium was measured in plasma and urine using flameless atomic absorption spectrophotometry, and pharmacokinetics of total and ultrafilterable gallium were calculated. Twenty-five patients with non-small cell lung cancer received 1–12 (median 2) courses of gallium nitrate every 2 weeks. Of 21 patients evaluable for response, 1 partial response was recorded, 4 patients had stable disease, and 16 had progressed. The most serious toxicities were renal impairment and optic neuritis. Hypocalcaemia was recorded in 3 patients. The mean C_{max} was 15.2 ± 3.1 μg/ml (range 9.5–21.2). Most gallium remained ultrafilterable for the first 10 h, after which plasma protein binding increased, and at 48 h only 11% was present as ultrafilterable gallium. The elimination profiles of both total and ultrafilterable gallium were biphasic, and the distribution phase consisted of ultrafilterable gallium, with a distribution half-life of 1.4 h. Total gallium plateaued at 1.9 μg/ml at between 8 and 12 h, and the estimated elimination half-life was 63 h. The elimination half-life of ultrafilterable gallium was 16.5 h. Inter- and intra-patient variability in pharmacokinetics was minimal. A mean of 50 ± 14% of the gallium dose was excreted in the urine within 48 h. A short infusion of gallium nitrate achieving high peak plasma concentrations results in little efficacy in non-small cell lung cancer.

Key words Gallium nitrate · Pharmacokinetics · Ultrafilterable · Non-small cell lung cancer

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Introduction

Gallium nitrate (NSC-15200) is a group IIIa metal salt that was entered into clinical trials on the basis of activity in solid tumour models in animals [1, 10]. Phase I studies demonstrated that myelosuppression was minimal, and nephrotoxicity was dose limiting with short infusions above 700 mg/m^2 [15, 19]. The nephrotoxicity was ameliorated with hydration and mannitol diuresis, or by giving the drug as a continuous infusion. Gallium nitrate also causes hypocalcaemia and is successfully used in the treatment of hypercalcaemia and bone metastases. [14, 23]. Antitumour activity of gallium nitrate was seen in epithelial ovarian cancer [16], advanced bladder carcinoma [6, 20, 21], and some lymphomas [12, 24, 25], but little activity was reported for squamous cell carcinoma of the cervix [17, 22], metastatic breast cancer [11], colorectal cancer [4] or small cell lung cancer [2].

The present study investigated the pharmacokinetics and activity of 700 mg/m^2 gallium nitrate when given as a 30-min infusion every 2 weeks in patients with advanced non-small cell lung cancer. This was a schedule investigated in phase I studies and was used to determine the efficacy of achieving high peak values with shorter infusion schedules [3].

Materials and methods

Patients

Eligible patients were required to have histologically proven metastatic or unresectable non-small cell lung cancer that was measurable or evaluable, an Eastern Co-operative Oncology Group (ECOG) performance status of 0–3, and no other serious illness or concomitant malignancy. Patients also must have had normal renal and hepatic function (serum creatinine <0.12 mmol/l and liver function tests <1.5 times the normal value), and pretreatment WBC $>4.0 \times 10^9$/l, neutrophils $>2.0 \times 10^9$/l, platelets $>100 \times 10^9$/l and haemoglobin >10 g/dl. The patients must not have received prior chemotherapy, and must have recovered from the toxicity of prior radiation therapy, with an interval of at least 4 weeks since prior radiotherapy. All patients gave written informed consent, and the study was approved by the Institutional Ethics Committee.

Drug administration

Gallium nitrate (NSC-15200) was provided by the Division of Cancer Treatment, National Cancer Institute, United States. Each vial contained 20 ml of a solution of 500 mg gallium nitrate, 575 mg trisodium citrate dihydrate, and sodium hydroxide to pH 6.0–7.0. The appropriate amount was diluted in 250 ml normal saline and given as a 30-min intravenous infusion at a dose of 700 mg/m^2. Patients were prehydrated with 1 l of normal saline over 2 h, then with 400 ml 10% mannitol over 30 min prior to gallium nitrate. Following gallium nitrate, patients received 500 ml normal saline over 1 h, then 1 l over 4 h, then 1 l over 6 h. In the absence of dose-limiting toxicity, it was planned to treat patients every 2 weeks.

Sampling and drug assay

Blood (10 ml) was sampled into heparinised tubes predose and at 0.25, 0.5 (end infusion), 0.75, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 24, 28, 32, 36 and 48 h for a maximum of 3 courses. Plasma was frozen at -70 °C until assay. Selected plasma samples were thawed and ultrafiltered prior to assay using millipore Ultrafree micropartition cones with a molecular weight cut-off of 30,000 D. Urine volume was measured in serial collections for 48 h and an aliquot was frozen at -70 °C until assay.

Gallium was measured in plasma and urine using a flameless atomic absorption spectrophotometry method that was modified from Newman [18]. Briefly, matrix-matched standards (75–600 ng Ga/ml) were prepared from a gallium standard solution (Aldrich, Milwaukee, USA), and samples and standards were diluted as required with a matrix modifier (adapted from Delves [7]), consisting of 0.11% w/v EDTA-diammonium salt, 0.33% w/v ammonium dihydrogen orthophosphate (both from BDH, Poole, UK), 0.1% v/v Triton X-100, with pH adjusted to 6.5 using ammonia solution (both from BDH, Kilsyth, Australia). All measurements were the means of triplicate analyses. Samples were analysed using a Perkin Elmer 3030 atomic absorption spectrophotometer with deuterium background correction, an AS-40 autosampler, HGA-400 graphite furnace, nitrogen as the inert gas, a gallium lamp from Photron, Narre Warren, Australia, and pyrolytically coated graphite tubes (Perkin Elmer). The sample volume was 10 µl, and the limit of detection was 20 ng/ml.

Pharmacokinetics

Standard pharmacokinetics were calculated either by non-compartmental analysis or by fitting a biexponential curve to the data (weighted 1/concentration^2) [8]. Parameters included distribution and elimination half-lives, the area under the curve using the trapezoidal rule from time 0 to 48 h (AUC_{0-48}), and for ultrafilterable gallium this was extrapolated to infinity (AUC_{0-inf}) using the last measured concentration divided by the elimination rate constant, clearance as dose divided by AUC_{0-inf}, and renal clearance was calculated by dividing the ultrafilterable plasma gallium AUC_{0-48} by the cumulative urinary excretion of gallium. Results are presented as mean $\pm$ SD unless otherwise noted.

Results

Clinical

A total of 25 patients received 1–12 (median 2) courses of gallium nitrate every 2 weeks (Table 1). Twenty-one patients were evaluable for response; 3 had died or were lost to follow-up prior to evaluation, and 1 was subsequently found to have had a non-Hodgkin's lymphoma. One partial response was recorded. Four patients had stable disease as their best response, while 16 others had progressive disease.

Table 1 Patient characteristics (*ECOG PS* Eastern Co-operative Oncology Group Performance Status)

Number entered	25
Median age (range) years	57 (39–88)
Sex	
Male	15
Female	10
ECOG PS	
0	4
1	13
2	6
3	2
Histology	
Squamous	10
Adenocarcinoma	7
Large cell	5
Undifferentiated	2
Other	1
Past treatment	
Surgery	9
Radiotherapy – Radical	10
– Palliative	12
Sites of disease	
Lung	21
Bone	8
Nodes	6
Liver	4
Adrenal	4
Skin	4
Brain	3
Pleura	1
Thyroid	1
Eye	1
Median number of courses (range)	2 (1–12)

The most serious toxicities were deterioration in renal function and optic neuritis (Table 2). One patient with diabetic renal disease who developed acute renal failure subsequently acquired an infection and died. In a further patient, poor renal function worsened after gallium and was associated with anorexia.

Optic neuritis developed in one patient after 10 courses of gallium, but was reversed following steroids after gallium had been discontinued. Hypocalcaemia was recorded in three patients with levels of 1.51 mmol/l, 1.98 mmol/l and 1.51 mmol/l (normal range 2.1–2.6 mmol/l). This reversed without clinical sequelae. One patient developed tinnitus.

Pharmacology

Total plasma gallium was measured for up to 3 courses in all 25 patients. The elimination profile was biphasic (Fig. 1), and a plateau concentration of 1.9 μg/ml was reached by 12 h (Table 3). The terminal elimination half-life calculated from the mean data for all patients was approximately 63 h, and since this was longer than the sampling time, other pharmacokinetic parameters could not be accurately calculated for total gallium. Ultrafilterable gallium was measured in selected plasma samples from 11 patients on their first course, and an example of a plasma elimination profile is shown in Fig. 1 (*inset*). Most gallium remained ultrafilterable for the first 10 h, after which protein binding increased, and at 48 h only 11% was present as ultrafilterable gallium. In 17 patients who received at least 2 courses, analysis by paired *t*-test showed no significant differences ($P > 0.05$) for total gallium for C_{max} (14.8 ± 3.0 and 14.9 ± 2.6 μg/ml) or $AUC_{0–48}$ (104.3 ± 13.4 and 107.2 ± 16.2 μg/ml h). Eight of these patients received a 3rd course, and the $AUC_{0–48}$ was 101.1 ± 17.7 μg/ml h. Similarly, the $AUC_{0–48}$ for ultrafilterable gallium in 8 patients on their first 2 courses was 63.9 ± 16.2 and 64.5 ± 14.5 μg/ml h.

A mean of 50 ± 14% (range 21–76%) of the gallium dose was excreted in the urine within 48 h. In nearly all patients, half of this was excreted within 6 h, and 76% within 12 h. The maximum urine concentration of gallium ranged from 40 to 196 μg/ml. Renal clearance accounted for 65% of total body clearance of ultrafilterable gallium in the 11 patients for whom this parameter could be measured.

Table 2 Highest grade of toxicity per patient (%)

Toxicity	Grade		
	1	2	3
Renal	12	–	4[a]
Optic neuritis	–	–	4
Anorexia	8	8	4
Tinnitus	–	–	4
Nausea and vomiting	29	25	–
Anaemia	21	21	–
Diarrhoea	21	12	–
Fatigue	21	8	–
Mucositis	4	4	–
Metallic taste	25	–	–
Thirst	8	4	–
Neuropathy	4	4	–
Dizziness	8	–	–

[a] Plus 1 death occurred (grade 5)

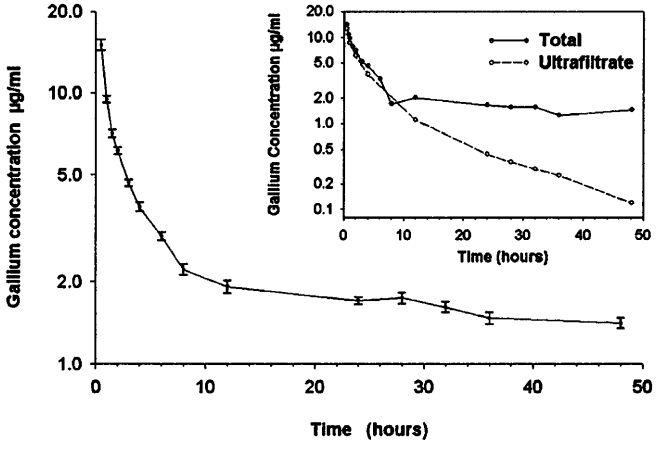

Fig. 1 Plot of total plasma gallium concentration versus time for all 25 patients on their first course of 700 mg/m^2 gallium nitrate intravenously over 30 min (mean ± SEM). *Inset*: Plasma concentration versus time for total and ultrafilterable gallium for 1 patient

Discussion

Gallium nitrate has little activity in non-small cell lung cancer in this trial, which confirms the results of an ECOG study, which recorded no responses in 14 patients [5]. Responses have been seen in bladder cancer [6] using a short infusion schedule, but more impressive responses have been recorded using continuous infusion schedules of gallium nitrate even in patients who had failed combination chemotherapy with methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) [20, 21]. Prolonged infusions are suitable for incorporating into

Table 3 Pharmacokinetics of total gallium in 25 patients and of ultrafilterable gallium in 11 of these patients receiving their first course of 700 mg/m^2 gallium nitrate

	Mean	SD	Range
Total gallium (n = 25)			
C_{max} (μg/ml)	15.2	3.1	9.5–21.2
Conc 12 h (μg/ml)	1.9	0.5	1.3–2.9
Conc 48 h (μg/ml)	1.4	0.3	0.8–2.1
$AUC_{0–48\ h}$ (μg/ml h)	106	14	80–134
Ultrafilterable gallium (n = 11)			
$AUC_{0–48\ h}$ (μg/ml h)	61	15	35–84
Clearance (ml/min)	88	28	56–160
Vd_{β} (l)	126	52	62–249
$t_{1/2}\ \alpha$ (h)	1.4	0.4	1.0–2.3
$t_{1/2}\ \beta$ (h)	16.5	5.4	6.6–26.5
Renal clearance (ml/min)	57	20	32–99

drug combinations, and these may be better for further testing of gallium nitrate in non-small cell lung cancer. As with other metal salts such as cisplatin, renal impairment is the most serious side effect. This can be alleviated by prehydration, extending the time between short infusions to 3 weeks or by infusing the drug more slowly [5, 20]. Reversible optic neuritis, however, still occurs with prolonged infusion schedules [20].

This trial is the first to report the pharmacokinetics of ultrafilterable gallium nitrate, while the results for total gallium and urinary excretion are comparable to previous studies. Hall et al. treated patients with 300–600 mg/m^2 and used a colorimetric assay to measure total gallium, reporting a biphasic curve with an initial half-life of 0.5–8 h, a terminal half-life of 10–50 h, and cumulative urinary excretion of 35% in 24 h [9]. Krakoff's group reported on three patients treated at 750 mg/m^2, and using atomic absorption (AA) spectrophotometry obtained a biphasic curve with an initial half-life of 87 min, terminal half life of 24 h and 65% excreted in the urine by 24 h [15]. Kelsen et al. studied two patients treated at 700 mg/m^2, and using AA to measure gallium, which was sampled for 96 h, obtained biphasic curves with initial half-lives of 8 and 26 min, terminal half-lives of 130 and 190 h, and $>49\%$ dose excreted in the urine [13].

Gallium binds reversibly to transferrin and exerts its antitumour effect by inhibiting cellular iron uptake. Transferrin is a plasma protein with a molecular weight greater than albumin, and would have been a component of the bound gallium fraction measured in the present study. However, gallium bound to transferrin is likely to be saturated, given the low concentration of transferrin in plasma compared with albumin (roughly 100 times less), and would not contribute significantly to the binding of the drug. The inter- and intra-patient variability in gallium pharmacokinetics is low, and gallium did not affect its own elimination when given every 2 weeks.

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