Randomized, Double-blind, Phase II Trial of Gallium Nitrate Compared with Pamidronate for Acute Control of Cancer-Related Hypercalcemia

a report by

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DOI: 10.17925/OHR.2006.00.01.76

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One of the most common serious metabolic disorder in cancer patients is hypercalcemia.[1] The highest incidence is observed in patients with widespread osteolytic bone metastases from multiple myeloma (MM) and breast cancer, followed by patients with epidermoid (squamous) carcinomas of the lung, and head and neck cancer. Effective treatment can reduce acute mortality, as well as improve quality of life; therefore, early intervention with highly potent agents can have a major impact on patient outcome. The bisphosphonates pamidronate is a potent inhibitor of bone resorption, and is widely used for to treat cancer-related hypercalcemia. Gallium nitrate has also shown high clinical activity, and the drug has been approved in the US for use in hypercalcemic patients who have not responded to hydration.

However, although gallium nitrate and pamidronate are both highly effective for acute control of cancer-related hypercalcemia, the proportion of patients who actually achieve normocalcemia has varied in published reports.[2,3-8] Due to heterogeneity of reported responses to pamidronate, the authors of this article conducted an exploratory, randomized, double-blind study to compare the efficacy and safety of gallium nitrate and pamidronate in hospitalized patients with cancer-related hypercalcemia.

Trial Design

The study was conducted at five centers in France and one center in the US. Eligible patients with hypercalcemia (defined as albumin-adjusted serum calcium 12.0mg/dL after intravenous hydration) were stratified on the basis of tumor histology (i.e. epidermoid or nonepidermoid) and by study site. Eligibility criteria included a histologic diagnosis of cancer; parenteral hydration 2,000mL for at least 24 hours preceding study entry; total corrected serum calcium adjusted for serum albumin 12.0mg/dL after hydration; serum creatinine 2.5mg/dL; no cytotoxic chemotherapy, plicamycin (mithramycin), or radiation therapy within the preceding seven days; no concomitant aminoglycoside therapy; and written informed consent. Patients receiving corticosteroids at the time of entry were eligible if the dose was stable or decreasing. No other hypocalcemic medications were allowed. Cytotoxic chemotherapy or radiation could not be administered during the five-day study period. Patients with hypercalcemia due to parathyroid carcinoma were ineligible, because there was no expectation that pamidronate would be useful. Patients with malignant lymphoma were excluded, because previously described antitumor effects of gallium nitrate in this disease could have biased the hypocalcemic response to that drug.[9] Patients were then randomly assigned to receive intravenous gallium nitrate 200mg/m2 daily for five days or intravenous pamidronate 60mg (increased during the study to 90mg for patients with initial serum calcium 13.5mg/dL) followed by placebo infusions for four days. The primary endpoint of the study was comparison of the proportion of patients who achieved normocalcemia.

Total serum calcium and creatinine were measured daily during the in-hospital treatment period and periodically thereafter. All values of serum calcium were adjusted for the most recent value of serum albumin using the following formula: corrected [Ca++] = uncorrected [Ca++] - [albumin] + 4.0.[10] Other blood tests that were monitored serially included a multichannel serum biochemical profile, serum electrolytes, hemoglobin level, and leukocyte and platelet counts. The presence or absence of bone involvement by tumor was assessed by radiography and/or scintigraphy.

Trial Results

In the study 64 patients were randomized. Both groups were similar with respect to age, gender, and tumor type (see *Table 1*), although there was a higher number of patients with epidermoid cancers in the pamidronate group. The pamidronate group had also received a greater amount of prestudy hydration. Conversely, there were more patients with extreme elevations of serum calcium in the gallium nitrate group. Mean serum creatinine was also higher in the gallium nitrate group.

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Table 1: Patient Characteristics at Baseline

	Gallium Nitrate (n=32)	Pamidronate (n=32)
Median age, y Sex, no.(%)	54	55
Male	16(50)	17(53)
Female	16(50)	15(47
Primary tumor, no. (%)		
Breast	11(35)	6(19)
Kidney	4(13)	1(3)
Head/neck	3(9)	9(28)
Lung	3(9)	4(13)
Myeloma	3(9)	0(0)
Other	8(25)	12(37)
Histology, no. (%)		
Epidermoid	9(28)	15(47)
Nonepidermoid	23(72)	17(53)
Serum calcium elevation, no. (%)		
≥13.5 mg/dL	21(66)	19(59)
> 16.0 mg/dL	6(19)	3(9)
Mean fluid intake, mL/d[a]	3,688	4,317
Mean serum creatinine ± SD, mg/dL	1.2 ± 0.6	1.0 ± 0.4
Mean serum phosphorus ± SD, g/dL	3.0 ± 1.1	2.7 ± 0.8

[a] Fluid intake recorded during 24 hours preceding protocol treatment.

Thirty-two patients received gallium nitrate, and 32 patients received pamidronate. Twenty-two patients (69%) who received gallium nitrate achieved normocalcemia compared with 18 patients (56%) who received pamidronate (see *Table 2*). Two patients from each treatment arm were removed during the course of the study and were declared protocol failures. Patients with initial serum calcium 13.5mg/dL who were treated with pamidronate did not respond better to 90mg (seven of 13 patients; 54%) than to 60mg (three of six patients; 50%). These response rates were lower than that achieved with gallium nitrate (15 of 21 patients; 71%) in patients with similarly severe hypercalcemia. The response to pamidronate was also inferior in patients with epidermoid tumors (33%) compared with the response in such patients to gallium nitrate (68%), whereas similar response rates were observed in patients with nonepidermoid tumors (76% for the pamidronate group, 70% for thegallium nitrate group). Although gallium nitrate was more effective in patients from both France and the US, the hypocalcemic response in French patients was inferior relative to that in US patients in both treatment groups (see *Table 2*). There were higher numbers of male patients and epidermoid cancers in the French study population.

Duration of normocalcemia was determined using an intent-to-treat (ITT) analysis that included all patients irrespective of response. The median duration of normocalcemia was one day in the pamidronate arm and seven days in the gallium nitrate arm. Normocalcemic duration was also estimated by an analysis including only complete responders that was censored for patients who had not experienced relapse within 20 days. In that analysis, the median duration of normocalcemia was 10 days for the pamidronate group and 14 days for the gallium nitrate group. Because hypercalcemia can be acutely life threatening, early mortality (deaths occurring 20 days from randomization) and overall mortality from all causes were analyzed. During the first 20 days, nine patients on the pamidronate arm died, compared with four patients on the gallium nitrate arm. Mortality information was available for 21 patients (66%) treated with gallium nitrate and 26 patients (81%) treated with pamidronate. The median overall survival times in these treatment groups were 39 days (gallium nitrate group) and 37 days (pamidronate group).

The use of pamidronate and gallium nitrate has been associated with renal insufficiency. As noted, patients treated with gallium nitrate entered the study with slightly higher mean serum creatinine values, and the differences observed at baseline were maintained during the period of observation. No patient in either treatment group developed acute renal failure during the trial. Hypophosphatemia (defined as a nadir value <2.5 mg/dL within four to eight days after randomization) was observed in 23 of 28 (82%) evaluable patients treated with pamidronate and in 23 of 26 (88%) patients treated with gallium nitrate. The median nadir value of serum phosphorus was 1.8 ± 0.7 for pamidronate and 1.6 ± 1.0 for gallium nitrate.

Discussion

The results of this study confirm that gallium nitrate is a highly effective therapy for acute control of cancer-related hypercalcemia. Previous studies of pamidronate have reported widely varying rates of response, from approximately 40% to 100%.[2-6] In this randomized, double-blind study of hospitalized patients, 69% of patients treated with gallium nitrate achieved normocalcemia, compared with 56% of patients treated with pamidronate. However, the response to pamidronate was particularly inferior in patients with epidermoid cancers, only 33% of whom achieved normocalcemia. Conversely, as in previous studies, the response to gallium nitrate appeared relatively uniform across patient subsets irrespective of histologic diagnosis or initial severity of hypercalcemia. In the study only patients who achieved normocalcemia were considered responders. Stringent criteria were also employed for determination of response duration. By ITT analysis, the median duration of normocalcemia was one day for pamidronate and seven days for

gallium nitrate. However, as noted elsewhere,[5] the ITT analysis may exaggerate differences where one treatment arm yields an inferior response rate. Thus, the responder-only analysis ignores the contribution of nonresponding patients and examines the response duration only in patients who have achieved normocalcemia. With this analysis, the median duration of normocalcemia was 10 days for pamidronate and 14 days for gallium nitrate.

Nonetheless, both the percent response and especially the reported duration of normocalcemia are notably lower in this study compared with other reports of bisphosphonate therapy. For example, in a recent trial comparing zoledronate and pamidronate,[5] the rate of normocalcemic response to pamidronate was 70%, and the estimated duration of normocalcemia was 17 to 18 days. However, it appears that response definitions account for most of the differences between these results and those of this present study. Specifically, normocalcemia in the zoledronate versus pamidronate study was defined as a serum calcium level ≤10.8mg/dL (compared with 10.5mg/dL in the present trial).

Moreover, the duration of normocalcemia was extended to the date on which serum exceeded 11.5mg/dL-a level well above the upper limit of normal - compared with ≥10.5mg/dL in this present trial. Thus, results from this present trial are congruent with data from other large studies of bisphosphonates, and the effects of gallium nitrate in this study are also consistent with previous reports for that drug. In summary, this randomized, double-blind, phase II study suggests that gallium nitrate is at least as effective as pamidronate for acute control of cancer-related hypercalcemia. These results also indicate that future studies of gallium nitrate might specifically target patient populations that fared poorly when treated with pamidronate in this trial, including those with epidermoid cancers, severe hypercalcemia at baseline, and disease that is poorly responsive or refractory to prior bisphosphonate therapy. ■

Table 2: Normocalcemic Responses in Patients Treated with Gallium Nitrate or Pamidronate

	Gallium Nitrate (n=32)	Pamidronate (n=32)
Overall response, no. (%)	22(69)	18 (56)
Response by tumor histology, no. (%)		
Epidermoid	6/9 (68)	5/15 (33)
Nonepidermoid	16/23 (70)	13/17 (76)
Response by country of origin, no. (%)		
United States	12/15 (80)	11/15 (73)
France	10/17 (59)	7/17 (41)
Response by initial serum calcium 13.5mg/dL, no. (%)	15/21 (71)	10/19 (52)
Pamidronate 60mg		3/6 (50)
Pamidronate 90mg		7/13 (54)

A complete account of this trial can be found in the Cancer Journal: Cvitkovic F, Armand J P, Tubiana-Hulin M, Rossi J F, Warrell R P Jr, "Randomized, double-blind, phase II trial of gallium nitrate compared with pamidronate for acute control of cancer-related hypercalcemia", Cancer J *(2006);12(1): pp. 47–53.*

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