

Treating Cancer-Related Hypercalcemia With Gallium Nitrate

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Hypercalcemia is the most commonly reported life-threatening metabolic disorder in patients with cancer, with an incidence estimated at 10% to 20% overall but varied greatly across tumor types (reportedly as high as 30% to 40% in patients with breast cancer, lung cancer, or multiple myeloma) [1–4]. Cancer-related hypercalcemia, with a prognostic factor for survival of less than 1 year [5], is particularly prevalent among patients with treatment-refractory advanced disease [4]. Patients with moderate-to-severe hypercalcemia, defined as a corrected (for albumin) total serum calcium level of 12–14 mg/dL, are likely to be symptomatic [3].

Manifestations of hypercalcemia may occur in virtually any organ system given the prominent role of calcium in maintaining cell membrane permeability and can easily be mistaken for underlying disease processes (including brain metastases) or anticancer therapy-associated toxicity. The clinical sequelae of hypercalcemia are not only potentially fatal but can also adversely impact quality of life, with a symptomatology that includes anorexia, nausea and vomiting, constipation, polyuria, bone pain, mental status changes, and lethargy.

In the pathogenesis of cancer-related hypercalcemia, the current understanding is that a) humoral factors released by tumor cells are primarily responsible for disrupting normal calcium homeostasis; and b) local factors secreted by tumor cells in bone play a contributory role by directly stimulating osteoclastic resorption [6]. These humoral and local factors ultimately accelerate osteoclastic bone resorption in conjunction with some degree of stimulation of calcium reabsorption from the renal tubules. In a study of 30 patients with solid

Abstract Gallium nitrate is an approved therapy for symptomatic, cancer-related hypercalcemia unresponsive to adequate hydration, the most common life-threatening metabolic disorder of cancer. Initially developed because of its antineoplastic properties, gallium nitrate demonstrated the ability to reduce serum calcium levels in early trials. Although the mechanism by which gallium nitrate corrects hypercalcemia is not fully understood, it appears to involve multiple effects (inhibition of osteoclast-mediated bone resorption, stimulation of bone formation, and alteration of the mineral composition and properties of bone); however, gallium nitrate is not cytotoxic to bone cells. In randomized trials for moderate-to-severe cancer-related hypercalcemia, gallium nitrate was well tolerated and produced a higher rate and longer duration of normocalcemia relative to calcitonin and the bisphosphonates etidronate and pamidronate. Gallium nitrate induced normocalcemia in 72% to 82% of patients; in contrast to the comparator agents, it was effective regardless of epidermoid tumor status. Epidermoid tumors are associated with high levels of parathyroid hormone-related protein (PTHrP), the principal mediator of cancer-related hypercalcemia in solid tumors. High levels of PTHrP appear to adversely impact the calcium-lowering potential of bisphosphonates. The recommended schedule of gallium nitrate for the treatment of cancer-related hypercalcemia is 200 mg/m² per day as a 5-day continuous intravenous infusion, administered with adequate hydration and close monitoring of renal function. Gallium nitrate is an effective treatment option for moderate-to-severe cancer-related hypercalcemia, a setting in which morbidity and mortality are high.

tumors who had humoral hypercalcemia, all patients had detectable or increased plasma levels of parathyroid hormone-related protein (PTHrP) [7]—now regarded as the principal mediator of cancer-related hypercalcemia in patients with solid tumors [4].

Despite advances in facilitating the diagnosis and treatment of cancer-related hypercalcemia, a recent prospective study found that less than 40% of hospitalized patients with cancer who developed hypercalcemia received specific hypocalcemic therapy [8]. Hypercalcemia-targeted intervention may be intentionally withheld in patients known to be suffering from rapidly progressive end-stage disease [3], but reducing the associated morbidity and mortality of hypercalcemia is desirable in most

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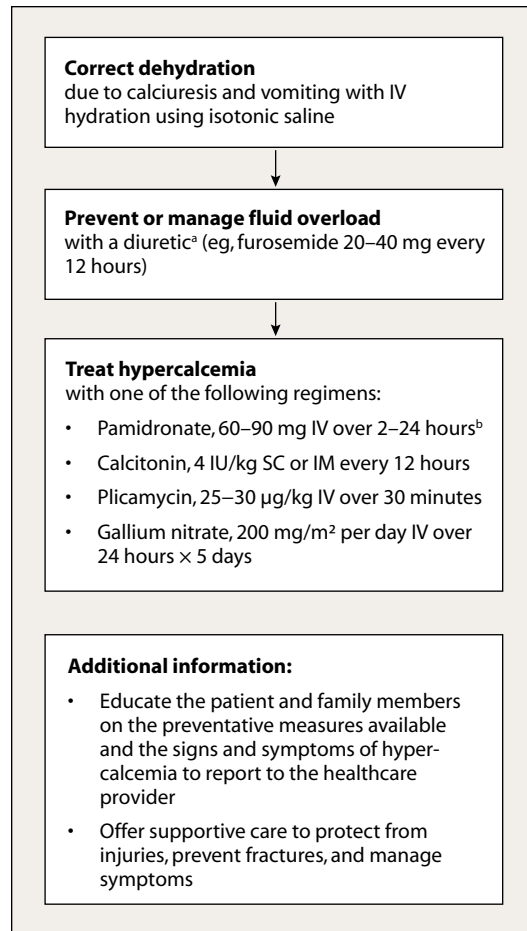


Figure 1 Management of Hypercalcemia

Treatment algorithm in the management of hypercalcemia. IV = intravenously; SC = subcutaneously; IM = intramuscularly

^aThiazide diuretics are contraindicated in this setting.

^bBased on data from randomized trials of pamidronate vs zoledronic acid in treating cancer-related hypercalcemia, zoledronic acid is the more effective second-generation nitrogen-containing bisphosphonate.⁹

cases. As patients typically exhibit dehydration at diagnosis of hypercalcemia, hydration via intravenous fluids is fundamental to initial management efforts [3]. Treating the underlying disease, albeit the most effective means of ameliorating cancer-related hypercalcemia, may not be feasible in the short or long term; therefore, normalizing serum calcium levels typically requires definitive pharmacologic therapy with the ability to inhibit bone resorption and further promote renal calcium excretion (ie, calciuresis) [6].

According to the National Cancer Institute (NCI), hypercalcemia should be treated with one of the following four agents (Figure 1): pamidronate, a second-generation nitrogen-containing bisphosphonate; salmon calcitonin; plicamycin (Mithracin), an osteoclast RNA synthesis inhibitor; or gallium nitrate (Ganite), the hydrated nitrate salt of the group IIIa element gallium [3]. Of note, a pooled analysis of two randomized trials found that the newer nitrogen-containing bisphosphonate, zoledronic acid (Zometa), was more effective than pamidronate in cancer-related hypercalcemia [9].

Gallium nitrate, initially evaluated by the NCI as an antineoplastic agent, was serendipitously found to induce transient hypocalcemia in cancer patients with previously normal serum calcium concentrations [10], prompting subsequent development of gallium nitrate as an antihypercalcemic agent [11].

Gallium Nitrate in Cancer-Related Hypercalcemia

Although gallium nitrate is believed to inhibit calcium resorption from bone, in vitro and animal studies have yet to precisely characterize its mechanism of hypocalcemic action. It is well established, however, that gallium nitrate is non-cytotoxic to bone cells and does not function as a metabolic toxin for osteoclasts [12]. In preclinical studies, gallium has been shown to preferentially accumulate in metabolically active regions of bone [12–15] and to exert a broad range of effects that include inhibition of osteoclast-mediated bone resorption (without general metabolic inhibition) [11, 16–18], stimulation of bone formation [19], and alteration of the mineral composition and properties of bone [12, 13, 15, 20, 21] (Table 1). There is evidence that bone-bound gallium reversibly and directly inhibits osteoclast activity [16, 22] via pH-dependent release of the

Table 1

Potential Mechanisms of Action for Gallium Nitrate in Hypercalcemia

INHIBITION OF BONE RESORPTION	EFFECTS ON BONE
Direct inhibition of osteoclast activity without general metabolic inhibition via pH-dependent release of gallium from bone mineral and inhibition of ATPase-dependent proton pump	Increased calcium and phosphorus deposition into bone Increased bone formation
Increased resistance to osteoclast-mediated resorption via enhancement of hydroxyapatite crystallization and reduction of bone mineral solubility	Potentially increased collagen synthesis Not cytotoxic to bone cells

Table 2**Comparative Trials of Gallium Nitrate in Cancer-related Hypercalcemia**

STUDY	REGIMENS	NORMOCALCEMIC RESPONSE RATE	MEDIAN DURATION OF RESPONSE (RANGE)
Warrell et al 1988 ²⁶	Gallium nitrate, 200 mg/m ² per day CIVI × 5 days	75% ^a (18/24)	6 days (1–15+ days)
	Calcitonin, 8 IU/kg IM every 6 h × 5 days	31% (8/26)	1 day (1–4 days)
Warrell et al 1991 ²⁷	Gallium nitrate, 200 mg/m ² per day CIVI × 5 days	82% ^b (28/34)	8 days (0–54+ days)
	Etidronate, 7.5 mg/kg per day 4-hr IV × 5 days	43% (16/37)	0 day (0–23+ days)
Bertheault-Cvitkovic et al 1996 ²⁸	Gallium nitrate, 200 mg/m ² per day CIVI × 5 days	72% (23/32)	NR (NR)
	Pamidronate, 60 or 90 mg 24-hr IV × 1 day ⇒ placebo infusions × 4 days	59% (19/32)	NR (NR)

Abbreviations: CIVI = continuous intravenous infusion; IM = intramuscularly; IV = intravenously; NR = not reported

^a Significantly ($P = 0.002$) greater than calcitonin

^b Significantly ($P < 0.001$) greater than etidronate

group IIIa element by osteoclastic acid, thereby auto-inhibiting the ATPase-dependent proton pump on the osteoclast “ruffled membrane” [22, 23]. Overall, gallium nitrate appears to have a multifaceted mechanism of action [24] that is distinct from the bisphosphonates and other hypocalcemic agents [17, 22, 23].

Randomized Trials in Moderate-to-Severe Hypercalcemia

The therapeutic potential of gallium nitrate for cancer-related hypercalcemia was evident in early open-label studies published during the mid-1980s [11, 25]. Subsequently, the relative efficacy of gallium nitrate versus calcitonin [26], etidronate [27], and pamidronate [28] in acutely controlling cancer-related hypercalcemia was evaluated in randomized, double-blind studies (Table 2). All three studies enrolled hospitalized patients with moderate-to-severe cancer-related hypercalcemia and used similar eligibility criteria, which included histologic diagnosis of cancers other than parathyroid carcinoma or malignant lymphoma; persistent elevation of total corrected (for albumin) serum calcium concentration ≥ 12.0 mg/dL; a serum creatinine level ≤ 2.5 mg/dL; and no cytotoxic chemotherapy, irradiation, or plicamycin within the previous 7 days.

Patients were required to receive intravenous (IV) hydration with or without diuretics for at least 1 day [28] or 2 days [26, 27] before entry, and no concomitant aminoglycoside therapy was permitted during the study periods. Supplemental

hypocalcemic medication was not allowed (with the exception of corticosteroids provided that the dose was stable or on a decreasing trend at the time of entry.) Normocalcemia, the primary outcome in each study, was defined as a normal serum calcium value that occurred no later than 7 days after treatment in the absence of additional hypocalcemic or systemic antitumor therapy. Patients with a decrease in serum calcium that did not reach the threshold for normocalcemia or patients who died during the study with documented hypercalcemia at the time of death were considered treatment failures.

Gallium Nitrate Versus Calcitonin

In the first comparative study of gallium nitrate for moderate-to-severe cancer-related hypercalcemia, conducted at Memorial Sloan-Kettering Cancer Center (MSKCC), 50 patients were randomized to receive gallium nitrate ($n = 24$) or calcitonin ($n = 26$) [26]. All patients received IV hydration for a 48-hour period, followed by gallium nitrate (200 mg/m² per day) as a 5-day continuous IV infusion or calcitonin (at the maximally recommended dose of 8 IU/kg intramuscularly) every 6 hours for 5 days.

Gallium nitrate and calcitonin induced normocalcemia in 75% (18 of 24) and 31% (8 of 26) of patients, respectively, with a significant ($P = 0.002$) between-group difference of 44% (95% confidence interval [CI], 19%–69%; Figure 2). Additionally, the median duration of normocalcemia of 6 days (range, 1–15+ days) in the gallium

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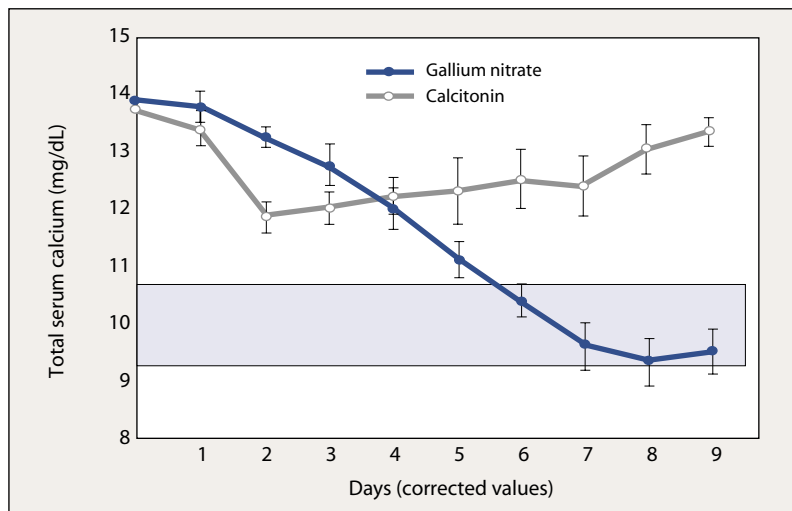


Figure 2 Results of Trial Comparing Gallium Nitrate Versus Calcitonin
Mean daily corrected serum calcium concentration in a comparative trial of gallium nitrate versus calcitonin (\pm SE). Shaded area indicates normal range for total serum calcium concentration. Used with permission from Warrell et al.²⁶

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nitrate group was significantly ($P < 0.001$) longer than the 1-day median duration (range, 1–4 days) seen with calcitonin. When less conservative criteria were used (in which serum calcium was not corrected for albumin and patients were not censored when cytotoxic or additional hypocalcemic measures were initiated), the median duration of normocalcemia was 11+ days with gallium nitrate versus 2 days with calcitonin ($P < 0.01$).

With pre-existing evidence suggesting greater resistance to hypocalcemic therapy among patients with epidermoid carcinomas (believed to commonly express PTHrP [7, 29, 30]), patients were stratified by epidermoid status prior to randomization [26]. Gallium nitrate induced normocalcemia in 75% (9 of 12) of patients in both the epidermoid and nonepidermoid subgroups, whereas corresponding response rates to calcitonin were 22% (2 of 9) and 44% (7 of 16), respectively. In both histologic subsets, gallium nitrate was significantly ($P = 0.0012$) more effective than calcitonin.

During the 5-day treatment period, no significant differences were observed between the 2 treatments in terms of fluid/diuretic use, median survival, or the proportion of patients experiencing improved mental/performance status. Of those patients with impaired mental status at baseline, 46% in the gallium nitrate group and 27% in the calcitonin group improved ($P = 0.16$); performance status improved in twice as many patients treated with gallium nitrate than with calcitonin (24% vs 12%; $P = 0.12$).

Two patients in the gallium nitrate group and one patient in the calcitonin group developed acute renal failure (incidences of 8% and 4%, respectively; $P > 0.4$); of note, one of the patients in the gallium nitrate group had a history of nephrectomy and received a gentamicin loading dose in violation of the study protocol. Between-group differences in mean serum creatinine values were not significantly different at any time. Mean serum phosphorus levels decreased in both groups to a similar degree. Reported adverse events were similar between the two groups, with the exception of a significantly higher incidence of asymptomatic hypophosphatemia with gallium nitrate (91% vs 45% with calcitonin; $P = 0.001$) and more nausea and vomiting with calcitonin (that approached but did not reach significance: 35% vs 14% with gallium nitrate; $P = 0.094$).

This comparative trial demonstrated that gallium nitrate was superior to maximally approved doses of calcitonin in acutely controlling cancer-related hypercalcemia. From a clinical practice standpoint, using calcitonin for hypercalcemia is limited by its short duration of action, with diminishing effects after 48 hours despite continued treatment [26, 31], as well as a high incidence of tachyphylaxis [3]. However, with a rapid onset of action occurring within 2 to 4 hours, calcitonin can be used as a bridge for lowering calcium levels within hours while awaiting the onset of a concurrently administered agent with less quickly attainable but more potent and/or prolonged hypocalcemic effects [3].

Gallium Nitrate Versus Etidronate

In a randomized, double-blind, multicenter study, 71 patients with moderate-to-severe hypercalcemia received gallium nitrate ($n = 34$) or the bisphosphonate etidronate ($n = 37$) [27]. At the time of the study, etidronate had just been approved for use in this setting. After stratification by epidermoid and performance status, patients were randomized to receive gallium nitrate at 200 mg/m² per day as a 5-day continuous IV infusion or etidronate at 7.5 mg/kg daily as a 4-hour IV infusion for 5 days.

Compared with etidronate, gallium nitrate was associated with a significantly higher rate of normocalcemia and longer duration of response, as well as significantly lower supplemental pharmacologic and fluid requirements. Normocalcemic response rates were 82% (28 of 34) with gallium

nitrate versus 43% (16 of 37) with etidronate ($P < 0.001$), lasting for a median of 8 days (range, 0–54+ days) versus 0 days (range, 0–23+ days), respectively ($P = 0.0005$). When evaluating responders only, the median response duration also significantly favored those treated with gallium nitrate, but to a lesser degree ($P = 0.04$). As additional evidence of persistent hypercalcemia among etidronate-treated patients, significantly more IV fluids ($P = 0.04$) were administered during the 5 days following completion of study treatment, and significantly more patients received additional hypocalcemic drug treatment during days 4 to 15 of the study (27% vs 9% with gallium nitrate; $P < 0.05$).

Mental status and performance status improved in 33% and 24% of gallium nitrate-treated patients, respectively, and in 38% and 16% of etidronate-treated patients, respectively, with no significant differences between the two groups. As noted by the investigators, the quality-of-life benefits were likely underestimated given that observations were censored when cytotoxic therapy was administered or hospital discharge occurred, thereby excluding some normocalcemic responders from the analysis.

Gallium nitrate was more effective than etidronate in all subgroup analyses (ie, histology, bone involvement, and severity of hypercalcemia; Figure 3). Gallium nitrate was associated with a 74% (14 of 19) response rate in patients with epidermoid tumors and induced normocalcemia in all but one patient with a tumor of nonepidermoid histology, for a response rate of 93% (14 of 15) in this latter subset. In both histologic subsets, less than half of the patients (43% per subgroup) attained normocalcemia with etidronate.

No treatment group differences were observed in mean daily serum creatinine levels or in the incidence of renal insufficiency, defined as serum creatinine ≥ 2.5 mg/dL irrespective of a possible relationship to treatment. Serum creatinine levels peaked no earlier than day 10 in all 5 patients with renal insufficiency in the gallium nitrate group; conversely, the peak occurred on or before day 7 in all 4 patients in the etidronate group. The investigators compared the rates of renal insufficiency—15% with gallium nitrate and 11% with etidronate—to those seen in patients ineligible for study participation who had moderate-to-severe hypercalcemia post hydration and concluded that the study treatments did not increase the rate of renal sufficiency

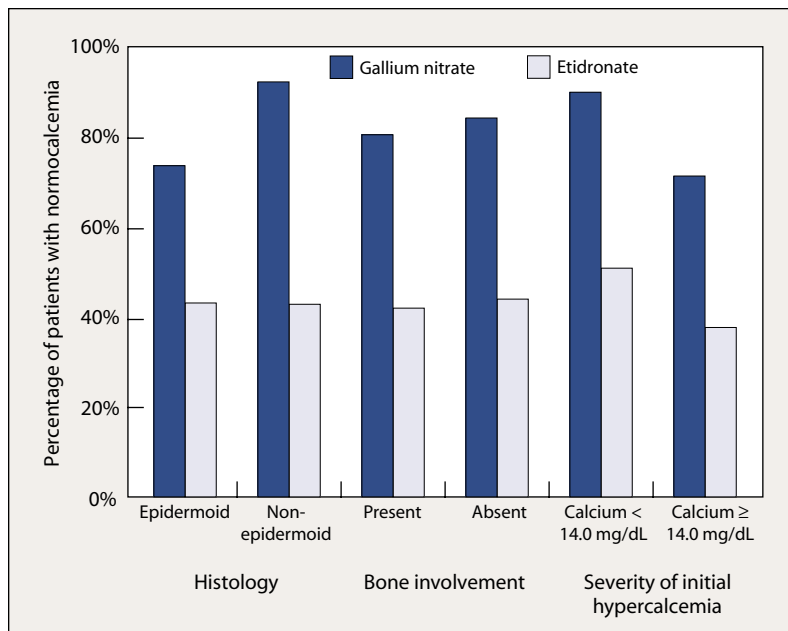


Figure 3 Results of Trial Comparing Gallium Nitrate Versus Etidronate

Subgroup analysis of normocalcemic response in a comparative trial of gallium nitrate versus etidronate. Data from Warrell.²⁷

(the incidence was 13% for the control group). Whereas the gallium nitrate group experienced a significantly higher incidence of asymptomatic hypophosphatemia (97% vs 43% with etidronate; $P < 0.001$), hyperphosphatemia was more commonly seen in etidronate-treated patients (11% vs 0% with gallium nitrate; P value not reported).

Gallium Nitrate Versus Pamidronate

The most recently conducted comparative trial of gallium nitrate for moderate-to-severe cancer-related hypercalcemia was an international trial in which 64 patients were randomized to receive gallium nitrate ($n = 32$) or pamidronate ($n = 32$) [28]. As in the prior studies, the gallium nitrate regimen was administered at 200 mg/m² per day as a 5-day continuous IV infusion. Pamidronate was administered as a 24-hour IV infusion followed by 4 days of placebo infusions, and patients were treated at one of two dose levels: 60 mg or 90 mg if serum calcium levels were < 13.5 mg/dL or ≥ 13.5 mg/dL, respectively.

Gallium nitrate was more effective than pamidronate in reducing serum calcium levels, producing a normocalcemic response rate of 72% (23 of 32) versus 59% (19 of 32) with pamidronate. Among patients with initial serum calcium levels ≥ 13.5 mg/dL, reflecting more severe cancer-re-

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Table 3**Gallium Nitrate Therapy: Practical Considerations**

Establish satisfactory urine output prior to instituting treatment with gallium nitrate.
Dosing of gallium nitrate: <ul style="list-style-type: none"> Usually given at the recommended dose of 200 mg/m² per day as a 5-day continuous IV infusion. Lower dose (100 mg/m² per day) can be considered in patients with mild hypercalcemia and minimal symptoms.
Hydration efforts: <ul style="list-style-type: none"> Adequate hydration is required during gallium nitrate therapy, defined as a minimum of 2,000 mL of oral or IV fluid. Overhydration can be problematic (particularly when cardiovascular status is compromised) and therefore must be avoided.
Promptly discontinue gallium nitrate if serum creatinine level exceeds 2.5 mg/dL, as the drug is contraindicated in patients with severe renal impairment (ie, serum creatinine level ≥ 2.5 mg/dL).
If use of a potentially nephrotoxic drug is necessary: <ul style="list-style-type: none"> Gallium nitrate should be discontinued. Continue hydration for several days after administration of the potentially nephrotoxic drug.
If hypocalcemia occurs, gallium nitrate should be stopped, and short-term calcium therapy may be required.
Gallium nitrate-related hypophosphatemia is typically of an asymptomatic and transient nature but may require oral phosphorus therapy.

IV = intravenously

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lated hypercalcemia, responses to pamidronate were similar between the two dose levels—54% and 50% for 60 mg and 90 mg, respectively—and were lower than the 71% response rate achieved with gallium nitrate. When comparing patients responding to gallium nitrate versus pamidronate, there was an equivalent likelihood of maintaining normocalcemia for at least 7 days. Patients treated with pamidronate had a 28% (9 of 32) mortality rate 3 weeks after randomization, as compared with 13% (4 of 32) mortality for patients treated with gallium nitrate (a proposed explanation for this apparent between-group disparity was not reported).

Gallium nitrate was more effective than pamidronate in patients with epidermoid cancers, with response rates of 68% versus 33%, respectively. In patients with nonepidermoid tumors, normocalcemic response rates were even higher and were similar between the two treatments: 73% for gallium nitrate and 81% for pamidronate (Data on file, Genta Incorporated).

Both drugs were characterized as well tolerated, with no significant nephrotoxicity in either group [28]. As expected based on prior experiences, gallium nitrate was associated with a significantly higher incidence of asymptomatic hy-

pophosphatemia than was pamidronate (Data on file, Genta Incorporated).

Consistent with the two fully published comparative trials [26, 27], gallium nitrate was more effective than pamidronate [28] in treating hypercalcemia. Currently, there is no evidence that any bisphosphonate is as effective as gallium nitrate in hypercalcemic patients with tumors of epidermoid histology. The efficacy of gallium nitrate in this subset of patients may be related to the high-level PTHrP expression characteristic of epidermoid tumors; this relationship is speculative, however, as levels of PTHrP were not directly measured in the clinical studies reported to date.

Practical Considerations

Gallium nitrate is indicated for symptomatic cancer-related hypercalcemia when initial hydration efforts are unsuccessful in restoring normal calcium levels. Practical considerations prior to and during gallium nitrate therapy are outlined in Table 3. Gallium nitrate has a long duration of action and may be discontinued as soon as normocalcemia is achieved—regardless of whether the 5-day course has been completed. When clinicians are faced with severe hypercalcemia, concurrent administration of calcitonin and gallium nitrate may be beneficial [4]; however, the relative merits of this combination over single-agent gallium nitrate have not been formally evaluated in a clinical trial.

In contrast to calcitonin and agents in the bisphosphonate class, comparative trials have demonstrated that gallium nitrate is effective regardless of epidermoid status (Table 4), providing suggestive evidence of activity against hypercalcemia mediated by high levels of PTHrP. Although etidronate was shown to be equally effective in patients with epidermoid versus nonepidermoid tumors, normocalcemic response rates in both histologic subsets were lower than those seen with gallium nitrate. Bisphosphonates appear to be less effective in hypercalcemic patients with high levels of PTHrP [32–34].

The continuous IV administration schedule of gallium nitrate is not as convenient as that of bisphosphonates. Hospitalized patients with moderate-to-severe hypercalcemia routinely receive IV fluids, however, negating the inconvenience of gallium nitrate therapy in an inpatient setting. In cases where outpatient therapy is desired, gallium nitrate can be administered via an ambula-

tory pump. If re-hydration does not produce an adequate response or if a bisphosphonate is selected as initial therapy but is ineffective in lowering calcium levels sufficiently, therapy with gallium nitrate is a reasonable option.

Gallium nitrate is well tolerated in patients with cancer-related hypercalcemia. The incidence of renal insufficiency with gallium nitrate in controlled studies was similar to that reported for comparator agents. Nonetheless, gallium nitrate has the potential to impair renal function, manifested by elevations in serum creatinine and blood urea nitrogen (BUN); concomitant use of gallium nitrate and other potentially nephrotoxic drugs may increase the risk of severe renal insufficiency. Other possible adverse effects include a decrease in serum bicarbonate, a decrease in blood pressure, anemia, and rarely optic neuritis, tinnitus, or partial loss of auditory acuity.

Summary

Gallium nitrate appears to have a multifaceted mechanism of action (directly inhibits osteoclast activity, increases calcium/phosphorus deposition into bone, and increases bone formation) without being cytotoxic to bone cells. This mechanism of action inhibits osteoclast-mediated bone resorption, which is the main process underlying the pathogenesis of cancer-related hypercalcemia. Clinically, randomized controlled trials have consistently shown that administering gallium nitrate 200 mg/m² per day as a 5-day continuous IV infusion is well tolerated and effective in treating moderate-to-severe cancer-related hypercalcemia. Normocalcemic response rates ranged from 72% to 82% for gallium nitrate versus 31% to 59% with the comparator agents, with the differences reaching significance in the two studies for which statistical differences were reported.

Duration of response likewise was considerably longer in gallium nitrate-treated patients. In the studies reporting this outcome, both using highly conservative criteria, median durations of response with gallium nitrate were 6 days and 8

Table 4

Responses in Comparative Trials of Gallium Nitrate by Tumor Histology

STUDY	HYPOCALCEMIC THERAPY	NORMOCALCEMIC RESPONSE RATE	
		EPIDERMOID	NONEPIDERMOID
Warrell et al 1988 ²⁶	Gallium nitrate × 5 days	75% ^a	75% ^a
	Calcitonin × 5 days	22%	44%
Warrell et al 1991 ²⁷	Gallium nitrate × 5 days	74%	93%
	Etidronate × 5 days	43%	43%
Bertheault-Cvitkovic et al 1996 ²⁸	Gallium nitrate × 5 days	68%	73%
	Pamidronate × 1 day	33%	81%

^aSignificantly greater than calcitonin, for both epidermoid ($P = 0.0012$) and nonepidermoid ($P = 0.0012$) tumors

days—starkly contrasting with the corresponding values of 1 day and 0 days for calcitonin and etidronate, respectively. Based on the comparative trial experience, gallium nitrate is more effective than any other hypocalcemic agent in patients with epidermoid tumors (histology associated with high-level PTHrP expression), generally producing normocalcemic response rates equivalent to those attainable in patients with nonepidermoid tumors.

In light of the prominence of PTHrP in mediating humoral cancer-related hypercalcemia in patients with solid tumors, these histologic findings are clinically relevant and justify consideration of gallium nitrate for management of this problem. Elevations in serum creatinine and BUN levels may occur during gallium nitrate therapy, but rates of renal insufficiency were low in the randomized trials and not greater than those seen with the comparator agents—possibly a consequence of proper patient selection, adequate hydration, and renal function monitoring. Gallium nitrate is an effective and well-tolerated option for managing symptomatic, cancer-related hypercalcemia that is unresponsive to adequate hydration and may also be useful in patients with an inadequate response to bisphosphonate therapy.

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Hypercalcemia and Gallium Nitrate

PEER VIEW POINT

Commentary by Harold A. Harvey, MD, and Salah M. Almokadem, MD

Tumor-related hypercalcemia is a well-recognized metabolic complication of several different types of malignancies. In recent years, however, the prevalence of this condition appears to be decreasing, in part due to more effective systemic cancer treatment and also to the more widespread use of bisphosphonates. The article by Dr. Leyland-Jones is a timely and thorough review of the clinical data supporting the use of gallium nitrate (Ganite) as therapy for tumor-related hypercalcemia. Gallium nitrate is a relatively effective treatment for malignancy-associated hypercalcemia but is little used because of the availability of other agents.

As noted by the author, hypercalcemia causes significant impairment of quality of life of patients with cancer. Symptoms of tumor-related hypercalcemia may be nonspecific, but early recognition and appropriate management can enhance the supportive care of critically ill patients. Treatment principles include vigorous hydration, treatment of the underlying malignancy, and use of antiresorptive agents. The author notes that the hypocalcemic effects of gallium nitrate are mediated by several different mechanisms that distinguish it from other agents [1]. However, most authorities believe that the action of gallium nitrate is principally antiresorptive and related to the effect of the drug on osteoclast function.

The phase III clinical trials reviewed by Leyland-Jones support the conclusion that gallium nitrate

PEER VIEWPOINT

Leyland-Jones

is more effective than calcitonin, etidronate, and possibly pamidronate and is associated with no greater overall toxicity. However, the review presents no comparable data or discussion about more potent bisphosphonates, such as zoledronic acid (Zometa) or ibandronate (Boniva). The median duration of normocalcemia induced by gallium nitrate was 6 to 8 days. This is longer than was reported with calcitonin and etidronate but is clearly inferior to the results recently observed for newer bisphosphonates [2].

The author suggests that gallium nitrate is more effective in treating hypercalcemia associated with squamous cell histologies, presumably because of higher levels of parathyroid hormone-related protein (PTHrP). Notably, the clinical trials did not have significant numbers of patients in whom serum PTHrP levels were directly measured, so this speculation is tentative at best. The author is dismissive of the issues of cost and the inconvenience of administering gallium nitrate as a 24-hour infusion over 5 days. These factors have become major practical concerns. A successful, randomized clinical trial comparing gallium nitrate with newer, more potent bisphosphonates as treatment of hypercalcemia is unlikely.

Early clinical experience with gallium nitrate suggested a significant potential for nephrotoxicity. The actual clinical trial data presented in this review show that rises in creatinine levels following the use of gallium nitrate as treatment for hypercalcemia are no greater than those seen following calcitonin or some bisphosphonates.

The review presents a somewhat outdated treatment algorithm. In our experience, calcitonin is now seldom used because of its generally transient effect, and plicamycin (Mithracin) has been removed from many hospital formularies. The availability of an agent such as zoledronic acid, which is highly effective, long acting, and

conveniently administered over 15 minutes, has significantly changed the relevance of the suggested algorithm. In clinical practice, resistance to zoledronic acid is relatively uncommon and can be managed by increasing the dose from 4 mg to 8 mg or by increasing the frequency of dosing. Nevertheless, faced with the clinical problem of refractory hypercalcemia, the availability of an effective agent with potentially different mechanisms of action would be useful.

This excellent review suggests that gallium nitrate could fill such a niche in the treatment of hypercalcemia of malignancy. Should the clinical trials of gallium nitrate cited by the author prove that the drug is an effective antineoplastic agent, it could become the drug of choice for treating hypercalcemia associated with sensitive tumor types, or malignancies where high serum levels of PTHrP can be shown to require this approach.

In current practice, based on considerations of efficacy, safety and convenience, zoledronic acid remains our drug of choice for treating tumor-related hypercalcemia. This article focusing on gallium nitrate does not provide a persuasive case for changing this practice.

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A second peer viewpoint on this article by Dr. Rasim Gucalp appear on page 518.

P E E R V I E W P O I N T

Commentary by Rasim Gucalp, MD

Dr. Leyland-Jones has presented an excellent review on the role of gallium nitrate (Ganite), a somewhat forgotten but effective agent in the treatment of tumor-induced hypercalcemia. However, during the past two decades, other effective and well-tolerated drugs, such as the bisphosphonates, which are more easily administered than gallium nitrate, have emerged as first-line treatment of tumor-induced hypercalcemia [1, 2]. Early randomized trials with gallium nitrate and pamidronate demonstrated not only the efficacy of both agents, but also the poor prognosis of patients with tumor-induced hypercalcemia [1, 3]. Control of hypercalcemia, even in terminal patients with cancer, may improve their quality of life and allow them to stay out of the hospital and spend their remaining time at home with their loved ones. Control of hypercalcemia also has been found to be beneficial in the inpatient hospice setting [4].

Bisphosphonates have proven to be effective inhibitors of bone resorption, particularly when administered intravenously [2]. The first generation bisphosphonates, etidronate and clodronate, are metabolized to non-hydrolyzable cytotoxic analogues of adenosine triphosphate. These molecules have cytotoxic effects on osteoclasts and can induce apoptosis [5].

The newer, nitrogen-containing aminobisphosphonates such as ibandronate (Boniva) and zoledronic acid (Zometa) have a different mechanism of action. They are not metabolized and inhibit farnesyl diphosphonate synthase, an enzyme in the mevalonate pathway. This enzyme prevents the synthesis of farnesyl diphosphonate and geranyl diphosphate, which are required for post-translational prenylation of small GTP-binding proteins. Loss of prenylation of these proteins prevents osteoclast formation and inhibits bone resorption [6]. These bisphosphonates also activate caspase-3-type proteases downstream of geranylation, resulting in apoptosis [7].

These newer, more potent aminobisphosphonates are more effective in the treatment of tumor-induced hypercalcemia [2, 8] and may increase the percentage of patients who can achieve normocalcemia [9]. There also is some evidence that these more potent bisphosphonates may increase time to relapse.

The study by Major and colleagues [2] was a pooled analysis of two randomized, double-blind studies comparing the efficacy and safety of zoledronic acid and pamidronate in the treatment of hypercalcemia; zoledronic acid was shown to be superior to pamidronate. Patients were randomized to receive 4 mg or 8 mg of zoledronic acid or 90 mg pamidronate. On day 10, 69.7% of patients who received pamidronate achieved a complete response, compared with 88.4% of patients who received the 4-mg dose of zoledronic acid and 86.7% of patients who received the 8-mg dose of zoledronic acid. Patients on zoledronic acid also experienced a longer duration of complete response, with a median duration of 32 days and 43 days for the 4-mg and 8-mg groups, respectively, compared with 18 days for those on pamidronate. Approximately 50% of patients who were refractory to initial therapy or who subsequently relapsed after initial treatment responded to treatment with zoledronic acid.

Despite the use of 90-mg pamidronate, a higher dose than used in previous studies, complete response rates were lower than those reported in two earlier studies [1, 10]. These lower rates may partially be explained by the lack of mandatory hydration in the studies reported by Major et al [2].

Other randomized, placebo-controlled trials have shown that bisphosphonates can significantly delay the onset of and reduce the incidence of skeletal complications in patients with breast cancer, multiple myeloma, prostate cancer, and other solid tumors [11–13]. Pamidronate decreased the incidence of hypercalcemia from 6% in the placebo arm to 1% in the bisphosphonate-treated arm, a significant reduction ($P = 0.02$).

In brief, bisphosphonates with rehydration is, at least in the United States, the standard of care for the treatment and prevention of tumor-induced hypercalcemia. Corticosteroids also may be helpful in patients with steroid-responsive tumors such as lymphoma and multiple myeloma.

WHAT ROLE FOR GALLIUM NITRATE?

Where does gallium nitrate fit in our treatment algorithm of hypercalcemia? An interim analysis of an international study comparing the efficacy of gallium nitrate versus pamidronate has been reported in abstract form [14]. After accrual of 64 patients, 23 of 32 patients (72%) on gallium nitrate achieved normocalcemia,

compared with 19 of 32 patients (59%) treated with pamidronate. A subset analysis revealed that the response to pamidronate was notably worse in patients with epidermoid malignancies (33%) than the response to gallium nitrate (68%). Dr. Leyland-Jones rightfully points out that gallium nitrate is effective regardless of epidermoid status, providing suggestive evidence of activity against hypercalcemia mediated by high levels of parathyroid hormone-related protein (PTHrP).

The effect of serum PTHrP on response to bisphosphonates has been a controversial issue. Wimalawansa [15] found that patients with the highest levels of PTHrP had a poorer prognosis with shorter duration of normocalcemia after pamidronate, and plasma levels did not correlate with baseline corrected levels of calcium. Other studies [16, 17] also have performed subgroup analyses and shown that serum PTHrP correlates with poor response to bisphosphonates. Many other studies, however, have not supported this observation [1, 10, 18].

In the largest study published to date, Rizzoli and colleagues [18] analyzed 315 hypercalcemic cancer patients before and after treatment with ibandronate. PTHrP levels did not have a significant effect on the response to ibandronate and did not affect the risk of recurrence of hypercalcemia. The lower response rates to pamidronate also may simply be related to previous exposure to bisphosphonates, since multiple bisphosphonates were available for clinical use at the time of the study. Body and colleagues [19] found that fewer patients responded to bisphosphonates with each successive episode of hypercalcemia: 10%, 31%, and 85% of patients failed to respond to bisphosphonate therapy after the first, second, and third episodes of hypercalcemia, respectively.

Gallium nitrate, despite its cumbersome administration, should be used in relapsed cases, particularly in patients with multiple recurrences of tumor-induced hypercalcemia. Efficacy of gallium nitrate as chemotherapy for various tumors needs to be determined in additional clinical studies. Although initial studies are encouraging [20, 21], the jury is still out.

OTHER STUDIES

The role of bisphosphonates in the prevention of bone metastases is being tested in current clinical trials. Recent preclinical research has shown that bisphosphonates also exhibit a po-

tent antitumor activity [6] and may be synergistic with some cytotoxic drugs. However, this hypothesis has not been tested widely in clinical trials.

In recent years, our knowledge of bone metabolism and bone metastasis has increased markedly. Maintenance of bone structure is dependent upon the balance between the regulation and activity of osteoblasts and osteoclasts. Excessive osteoclastic activity is responsible for the production of lytic metastases and tumor-induced hypercalcemia. The development of active osteoclasts requires interaction between osteoblastic stromal cells and osteoclast precursors of the monocyte/macrophage lineage.

A large number of hormones and cytokines are known to influence osteoclast formation and activity, including parathyroid hormone (PTH); PTHrP; 1,25-dihydroxyvitamin-D₃; interleukin-6 (IL-6); IL-11; prostaglandin E₂; and macrophage colony-stimulating factor (M-CSF). These factors are unable to mediate osteoclast differentiation in the absence of osteoblastic stromal cells; the receptor activator of nuclear factor-κB ligand (RANKL) is a member of the tumor necrosis factor (TNF) ligand family, produced by osteoblastic stromal cell as well as T cells. RANKL acts upon its receptor, RANK, in mononuclear cells to induce differentiation to osteoclasts and maintain their activities. Osteoprotegerin is a soluble TNF-receptor molecule and demonstrates specific inhibition of osteoclast differentiation by acting as a decoy receptor for osteoprotegerin ligand (OPG-L or RANKL) [22]. Targeting RANKL as a therapeutic approach for cancer-related bone disease is intriguing.

Recombinant OPG construct (AMGN-0007) has shown promising results in a phase I trial [23]. A single dose of AMGN-0007 suppressed bone resorption in patients with multiple myeloma and patients with breast carcinoma. Changes were comparable to those with pamidronate. Similarly, monoclonal antibodies against PTHrP are undergoing clinical trials [24]. Thus, in the near future, we will be able to use targeted therapies to prevent and treat bone metastasis and its complications, such as tumor-induced hypercalcemia.

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