Skeletal Complications of Malignancy

Supplement to ***Cancer***

Gallium Nitrate for the Treatment of Bone Metastases

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Gallium nitrate was originally developed as an antineoplastic agent; however, further studies have revealed that this drug has extremely potent effects on turnover of bone, and that low doses can be used to reduce bone resorption. Like the bisphosphonates, gallium nitrate has been studied in both malignant and in nonmalignant conditions. The results of randomized double blind studies have suggested that this drug has superior clinical efficacy relative to etidronate, calcitonin, and pamidronate for the acute control of cancer-related hypercalcemia. In patients with Paget's disease, low doses of gallium nitrate reduce biochemical parameters of accelerated bone turnover, including urinary excretion of calcium, hydroxyproline, and urinary collagen cross-linked N-telopeptides. Preliminary studies showed similar effects in patients with bone involvement from a wide variety of tumor types. Based on this high degree of clinical potency revealed in clinical studies, two randomized Phase III studies have been initiated in patients with bone metastases from breast carcinoma and bone involvement due to multiple myeloma. Both studies employ cyclic therapy with low dose gallium nitrate (i.e., 40 mg administered as a subcutaneous injection once daily for 2 weeks, followed by 2 weeks off treatment, recycled monthly). The endpoints of both studies are to document reductions in time to ''morbid skeletal events,'' such as palliative skeletal radiotherapy, stabilizing orthopedic surgery, or pathologic fractures, as well as decreases in pain and analgesic requirements and improvements in mobility and other aspects of quality of life. These trials should provide definitive evidence of whether this agent is safe and effective as a treatment for bone metastases. ***Cancer* 1997;80:1680–5.** *©1997 American Cancer Society.*

Elemental gallium is a potent inhibitor of bone resorption that acts to maintain or restore bone mass. By virtue of these biologic effects, gallium compounds are potentially useful treatments for a variety of diseases that are characterized by accelerated bone loss, including cancer-related hypercalcemia, bone metastases, Paget's disease, and postmenopausal osteoporosis. In this article, laboratory and clinical studies that support the use of gallium compounds as a treatment for bone metastases are reviewed.

Historical Aspects

In the late 1960s after the anticancer activity of platinum compounds was recognized,[1] a number of metallic elements were studied for their anticancer effects by the U.S. National Cancer Institute. All Group IIIA elements (such as boron, aluminum, gallium, and thallium) displayed substantial cytotoxic activity. Gallium was the most active and least toxic of these agents when tested against experimental animal tumors, and it was the only element in the group that was effective when inoculated at a site remote from the tumor (i.e., intraperitoneal injections were active against blood-borne leukemias, etc.).[2,3] Moreover, the ion to which the element was complexed (e.g., citrate, nitrate, chloride, acetate, etc.) was immaterial. Therefore, gallium nitrate solu-

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bilized with sodium citrate was selected to undergo animal toxicologic testing, and this agent eventually entered clinical studies in 1976. In these early studies as an anticancer drug, very high (''maximally tolerable'') doses were employed, and toxic effects were similar to those observed with cisplatin: nausea, emesis, and renal insufficiency. However, with the prominent exception of malignant lymphoma,[4,5] the drug has not exhibited significant anticancer activity in humans. Although some antineoplastic use of the agent continues (particularly for chemotherapy-refractory or acquired immunodeficiency syndrome-related lymphomas), this use largely has been abandoned.

One prominent side effect in early studies was hypocalcemia,[6,7] which was on occasion sufficiently severe to cause transient tetany.[4] One report using a rodent model suggested that this effect was caused by induction of hypercalciuria.[7] However, we subsequently showed that gallium-related hypocalcemia in fact was associated with a marked reduction in urinary calcium excretion.[8] This finding was the first suggestion that gallium might directly inhibit bone resorption, and further studies have since confirmed this early speculation.

PRECLINICAL STUDIES

Skeletal Localization

Gallium has certain physicochemical properties that are relevant to bone physiology. Elemental gallium in plasma precipitates in the presence of phosphate at pH $\geq$ 5.0, forming various metal/cation complexes of gallium-phosphate. Gallium readily adsorbs to hydroxyapatite, and it is rapidly incorporated into osteogenic foci[9] and within cells in metabolically active tissues.[10] Therapeutic doses of gallium result in trace level (i.e., parts per million) accumulation in bone.[11,12] Although quantification and localization of gallium in bone tissue posed a significant technical challenge, satisfactory spatial resolution of gallium was ultimately achieved using a method that employs a synchrotron to generate densely collimated beams of high energy X-rays and microscopic X-ray fluorescence detection.[13] In such studies, the highest gallium content was measured in the metaphyseal region of bone, notably in the epiphysis, whereas low levels of gallium were found in midcortical regions, which are only slowly remodeled.

Mineral Effects

Elemental gallium alters the mineral, matrix, and cellular properties of bone. X-ray diffraction analysis of bone powder from gallium-treated rats showed changes characteristic of an increase in either the size or crystalline perfection (i.e., the physical compaction) of hydroxyapatite mineral.[11] Infrared spectroscopy also suggested that carbonate content was decreased.[11] These changes were associated with a marked decrease in the physicochemical solubility of gallium-treated bone mineral compared with untreated controls.[12] Bone particles taken from the metaphyseal regions of animals treated in vivo with gallium nitrate showed an increase in bone density, a higher rate of new calcium accretion into bone, and an increased bone calcium and phosphate content.[12] These findings suggested that the potency of this agent may be due to dual effects on both decreased resorption and increased formation.

Cellular Effects

In addition to reductions in gross physicochemical solubility, bone treated with gallium nitrate is significantly more resistant to cell-mediated osteolysis. Fetal rat bones labeled in utero with ^{45}Ca demonstrated a dose-dependent inhibition of calcium release over a broad range of gallium concentrations (10–200 μM).[14] Gallium nitrate also significantly decreased bone resorption induced by parathyroid hormone and tumor necrosis factor.[14,15]

One model of in vivo resorption employs subcutaneous implants of bone pellets taken from rats treated in vivo with a test agent, and the time to implant disappearance then is measured, which is effected by local recruitment of mononuclear cells. In this model, a significant delay in resorption was observed for bone pellets excised from gallium-treated rats compared with untreated controls. Histologic sections of bone explants from gallium-treated rats have shown no changes in morphology relative to normal controls– and specifically no cytotoxic effects. Over the therapeutic range of concentrations, gallium did not alter DNA or general protein synthesis in bone explants or osteoblast cell lines.[16]

Gallium was shown to significantly enhance the synthesis and content of Type I collagen,[17] the major protein found in skeletal matrix. This observation also implied a salutary effect on bone formation, but it also might have indicated that nonmineralized protein was being formed, which would ultimately compromise the tensile strength of bone. Therefore, standardized biomechanical tests of bone strength were performed by subjecting bone from gallium-treated animals to torque stress. In these tests, no decrease in bone strength was observed compared with untreated animals.[18] Finally, Blair et al.[19] showed that elemental gallium in bone significantly decreased energy-dependent proton transport by osteoclasts. This effect currently is believed to be the principal mechanism by which this drug inhibits bone resorption.

CLINICAL STUDIES

Human Pharmacokinetics

After parenteral injection, gallium binds to a variety of plasma proteins, notably transferrin.[20] The half-life in plasma ($T_{1/2beta}$) is approximately 12 hours[7,21,22]; however, the terminal half-life is highly dependent on the method of administration. When administered by prolonged intravenous infusion or repeated subcutaneous injection, the plasma half-life increases significantly[23]—a difference that most likely reflects release from a deep tissue compartment (presumably bone). Skeletal tissue reversibly accumulates gallium in a dose-dependent manner.[10,11] The kidney is the major route of excretion, and renal clearance is not affected by hydration or diuresis.[4,7]

Studies in Cancer-Related Hypercalcemia

As a model for loss of neoplastic bone mass, cancer-related hypercalcemia obviously represents an extreme example. However, biochemical factors that cause this condition also are critical to the development and progression of bone metastases. As a consequence, inferences regarding pharmacologic activity in this disorder are probably representative of relative clinical potency in other skeletal diseases that are characterized by accelerated loss of bone mass. In early studies, we showed that continuous intravenous infusions of gallium nitrate at doses ranging from 100–200 mg/m^2 for 5–7 days induced normocalcemia in a very high proportion of hypercalcemic patients.[14,24] (Note that the effective dose in hypercalcemia was approximately one-third of that used in trials as an antitumor agent.[5])

Subsequently, gallium nitrate was compared with calcitonin in a randomized double blind trial of hospitalized patients with moderate-to-severe hypercalcemia who were relatively resistant to parenteral hydration. Overall, 75% of patients who received gallium nitrate achieved normocalcemia compared with only 27% of patients who received calcitonin ($P < 0.0006$).[25] Response criteria in this study were quite stringent (i.e., intent-to-treat analysis, no exclusions, and adjustments of all serum calcium levels for serum albumin concentrations).

Gallium nitrate proved highly effective for the treatment of hypercalcemia in two patients with virulent hypercalcemia due to parathyroid carcinoma.[23] Shortly thereafter, epidermoid (squamous) carcinomas were found to be highly associated with elevated plasma levels of the potent bone-resorbing substance, parathyroid hormone-related protein (PTH-rP).[26,27] In the randomized studies of gallium nitrate, all patients were stratified by tumor histology, given the antecedent perception that hypercalcemia due to epidermoid carcinoma was substantially more resistant to treatment and more likely to be ''humorally'' mediated. In the initial randomized study, only one of ten patients with epidermoid cancers treated with calcitonin achieved a normal serum calcium, whereas the response to gallium nitrate was independent of histology and patients with epidermoid and nonepidermoid tumor types responded equally well.[25]

Two other sequentially conducted studies have blindly compared gallium nitrate with various bisphosphonates. In the first study, gallium nitrate was compared with 5 daily infusions of etidronate (5 mg/kg/day). As shown in Figure 1, 82% of patients who received gallium responded compared with 43% of patients who received etidronate.[28] The duration of normocalcemia was also significantly longer for gallium-treated patients. Finally, an interim analysis of an international collaborative study comparing the relative effectiveness of gallium nitrate with pamidronate was recently reported.[29] After accrual of 64 patients, 23 of 32 patients (72%) treated with gallium nitrate achieved normocalcemia compared with 19 of 32 patients (59%) treated with pamidronate. As in the etidronate study, a subset analysis revealed that the response to pamidronate was notably worse in patients with epidermoid malignancies (33%) compared with the response to gallium nitrate (68%). These early data also suggested a benefit in reduction of early mortality (defined as death from any cause within 3 weeks from entry [28% with pamidronate vs. 13% with gallium nitrate].[29]

Thus, these clinical studies have confirmed in vitro observations that gallium antagonizes bone resorption irrespective of mechanism or cancer type. Based solely on clinical potency, gallium nitrate appears to be the most effective drug in clinical use for the treatment of cancer-related hypercalcemia. It appears to be the drug of choice for patients with osteolysis mediated by PTH-rP in which the response to bisphosphonates is demonstrably inferior.[30]

Studies in Bone Metastases

A variety of drugs that retard bone resorption have been proposed for adjuvant use in patients with bone metastases, including bisphosphonates, fluorides, and calcitonin. The dual actions of gallium to both decrease bone resorption and enhance new bone formation has suggested that this agent also might be useful for restoration of bone integrity in this condition.

In a preliminary study, gallium nitrate was administered by continuous intravenous infusion to 22 patients with lytic bone metastases. Examining commonly accepted parameters of bone turnover,

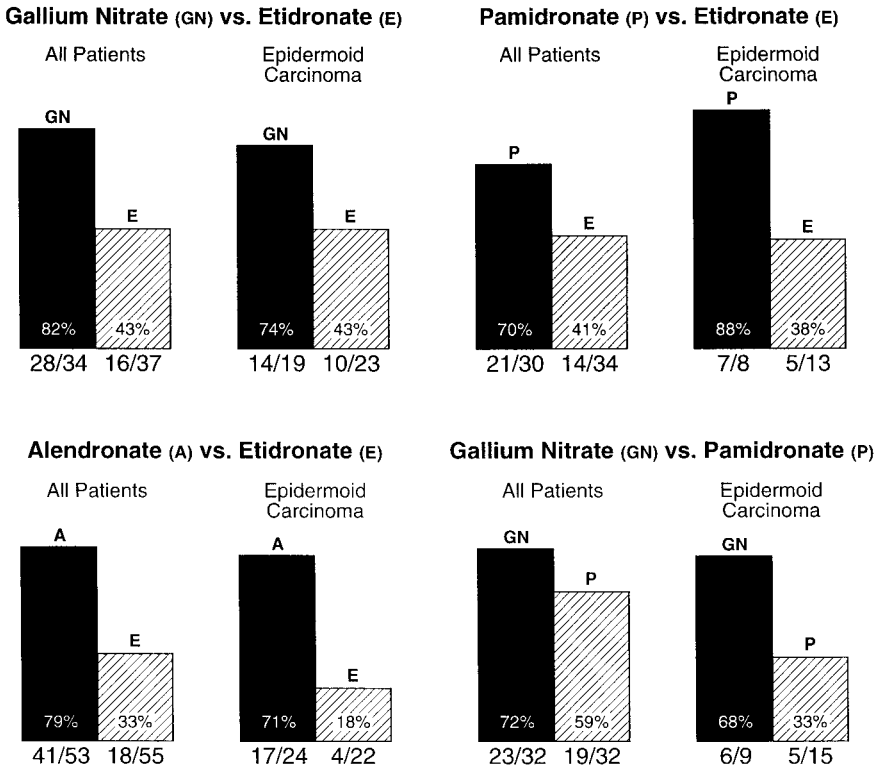

FIGURE 1. Results from four randomized double-blind comparisons of the major drugs used for acute treatment of cancer-related hypercalcemia. Bars depict proportions of patients who achieved a normal serum calcium value subsequent to treatment with the assigned agent. All analyses are based on "intent-to-treat." Numbers at bottom indicate number of patients responding over number of patients treated per group. The test drugs were administered on the following dose schedules: Top left: gallium nitrate (200 mg/m^2) as a continuous intravenous (i.v.) infusion daily for 5 days, and etidronate (7.5 mg/kg) as a 4-hour infusion daily for 5 days[28]; top right: pamidronate (60 mg) as a single 24-hour infusion, and etidronate (7.5 mg/kg) as a 4-hour infusion daily for 3 days; bottom left: alendronate (10 or 15 mg) as a single 2-hour infusion, and etidronate (7.5 mg/kg) as a 4-hour infusion daily for 3 days; bottom right: gallium nitrate (200 mg/m^2) as a continuous i.v. infusion daily for 5 days, and pamidronate (60 or 90 mg) as a single 24-hour infusion.[29] Reprinted with permission from Warrell RP Jr. Metabolic emergencies. In DeVita VT Jr., Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology. 5th edition, pages 2486–500, with permission of the publisher, J.B. Lippincott Co., ©1997.

urinary calcium excretion was significantly reduced in 21 of 22 patients, and urinary hydroxyproline excretion was lowered in patients with high basal levels of excretion.[31] Similar findings also were observed in patients with osteoblastic disease related to prostate carcinoma.[32]

Based on these data, a follow-up study was initiated in patients with multiple myeloma. Eligible patients were required to have achieved a "plateau" in their disease with standard anticancer treatment, and then were randomly assigned to receive standard therapy with or without low dose gallium nitrate for 6 months. Patients initially randomized to observation were crossed over to receive gallium nitrate after 6 months. The principal outcome determinant was the measurement of total-body calcium content using delayed gamma neutron activation analysis.[33]

As shown in Figure 2 patients who received gallium nitrate showed a substantial increase in total-body calcium relative to untreated controls. The increase was usually (although not uniformly) observed after 6 months of treatment. Most patients also experienced substantial relief of bone pain while receiving gallium. Clinically apparent pathologic fractures, along with one episode of hypercalcemia, were observed only in patients who initially were randomized not to receive gallium treatment.[34] These results suggested that prolonged treatment with gallium nitrate can be effective in reducing the morbidity associated with bone metastases.

Two follow-up studies were initiated in 1995 in patients with bone involvement from myeloma and breast carcinoma, respectively. In each study, patients who are receiving standard anticancer treatment are randomized to receive 6 months of low dose gallium nitrate (40 mg per day, 2 weeks on/2 weeks off) by subcutaneous injection or to placebo. Outcome determinants include comparisons of fracture incidence, subjective pain, analgesic intake, mobility, and quality of life. No results currently are available from these pivotal Phase III trials.

Conclusions

Gallium nitrate appears to be a uniquely acting agent for the treatment of bone-resorptive diseases. Although this activity was found incidentally to its original therapeutic purpose, extended studies using considerably lower doses indicates that this agent is a safe and highly

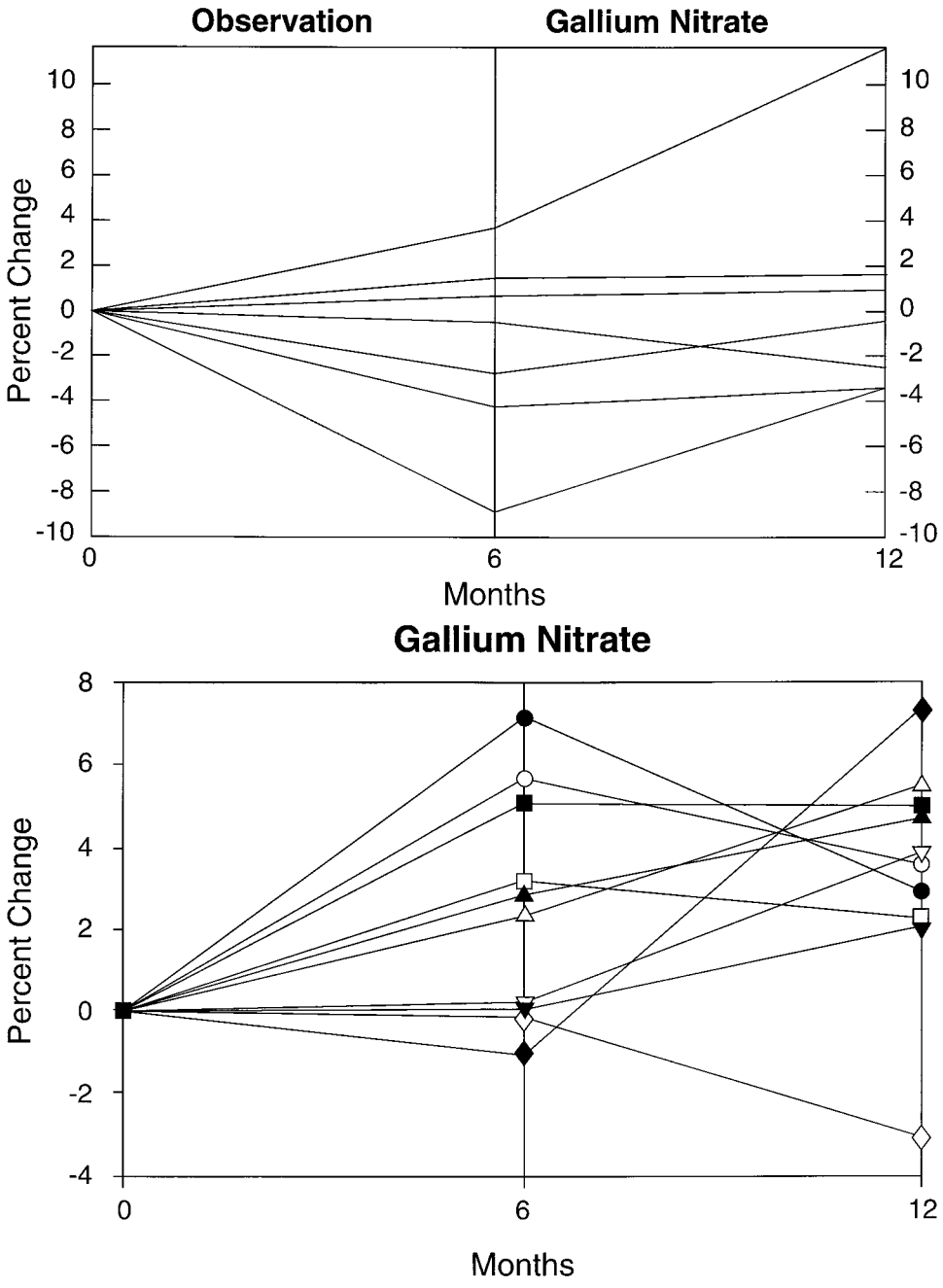

FIGURE 2. Changes in total body calcium as measured by delayed-gamma neutron activation analysis. The top panel shows changes in the subgroup of patients who were observed for 6 months (n = 7) compared with the second 6-month period during which they received treatment with gallium nitrate. The bottom panel shows the changes at 6 months and 12 months in patients from this series who continued to receive extended gallium nitrate treatment (n = 10). (Absolute values are normalized to 0 for each individual's baseline value.) Reprinted with permission from Warrell RP Jr., Lovett D, Dilmanian FA, Schneider R, Heelan RT. Low-dose gallium nitrate for prevention of osteolysis in myeloma. Results of a pilot randomized study. *J Clin Oncol* 1993;11:2443–50 ©1993, W.B. Saunders Co.

effective method of reducing accelerated bone loss in patients with cancer and metabolic bone disease. Additional studies are underway to identify orally active gallium-containing compounds that can be used for extended periods in benign metabolic bone diseases.

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