

Gallium Nitrate in Multiple Myeloma: Prolonged Survival in a Cohort of Patients With Advanced-Stage Disease

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Multiple myeloma is characterized by bone destruction mediated by osteoclastic bone resorption. Skeletal complications of myeloma, including bone pain, fractures, spinal cord compression and hypercalcemia, result in significant morbidity. Gallium nitrate was shown in a small, randomized trial to attenuate the rate of bone loss in patients with myeloma treated with chemotherapy. In a retrospective analysis, we found that patients with advanced multiple myeloma treated with chemotherapy plus gallium nitrate had markedly prolonged median survival compared with similar patients treated with chemotherapy alone (87+ months v 48 months, respectively). These data suggest that gallium nitrate may have a positive, indirect benefit on survival in myeloma by decreasing the rate of bone resorption. Further evaluation of gallium nitrate to attenuate progression of disease in patients with multiple myeloma is warranted.

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MULTIPLE MYELOMA is an incurable hematologic cancer involving clonal expansion of plasma cells in the bone marrow.¹ Unlike other hematologic diseases in which bone involvement is uncommon, bone destruction and skeletal complications are highly prevalent in patients with multiple myeloma (Fig 1).²⁻⁴ Bone pain, fractures, spinal cord compression, and hypercalcemia produce significant morbidity and adversely affect quality of life.^{1,2,5} Although bone lesions associated with multiple myeloma can occur in several different patterns, most patients have multiple, discrete osteolytic lesions that occur adjacent to nests of myeloma cells which display uncontrolled growth and secrete mediators of bone resorption.³ Bone destruction in patients with multiple myeloma is mediated by a dysregulation of osteoclasts.^{3,4} Increased osteoclastic resorption appears to be induced by a variety of factors produced by

the malignant myeloma cells and possibly other cells in the local marrow microenvironment in response to the tumor cells.^{3,4}

During normal conditions, bone homeostasis is a highly regulated process with a balance between bone-forming osteoblasts and bone-resorbing osteoclasts.⁶ One of the primary osteoclast-activating factors is tumor necrosis factor-related activation-induced cytokine (TRANCE), a member of the tumor necrosis factor (TNF) superfamily.⁷ TRANCE, expressed on the surface of osteoblasts, acts by binding to its functional receptor (TRANCE-R, also called RANK) that is expressed on osteoclasts. The binding of TRANCE to its receptor induces the differentiation and activation of osteoclasts from immature precursors. In addition, TRANCE appears to be both necessary and sufficient for hormone-mediated activation of mature osteoclasts.⁷ The key negative regulator of osteoclasts appears to be osteoprotegerin (OPG), a soluble receptor for several TNF family members.⁶ Osteoprotegerin is secreted by osteoblasts and binds to TRANCE, inhibiting TRANCE-induced osteoclast development. In transgenic mice, overexpression of OPG is associated with profound osteopetrosis that coincides with an inhibition of osteoclast maturation.⁶

Multiple myeloma patients exhibit a profound dysregulation of the TRANCE-OPG axis.⁸ Patients with myeloma overexpress TRANCE when compared with normal individuals. Conversely, myeloma-infiltrated marrows exhibit decreased expression of OPG. It remains to be determined if the overexpression of TRANCE seen in myeloma patients depends directly on the neoplastic cell or is the result of cell-stroma interactions.⁸⁻¹⁰

GALLIUM NITRATE IN MULTIPLE MYELOMA

Antiresorptive agents are currently incorporated into most treatment regimens for patients with multiple myeloma to decrease skeletal complications and improve quality of life.¹ The bisphosphonate pamidronate has been shown to be effective in reducing skeletal events in patients with advanced multiple myeloma.¹¹ In a random-

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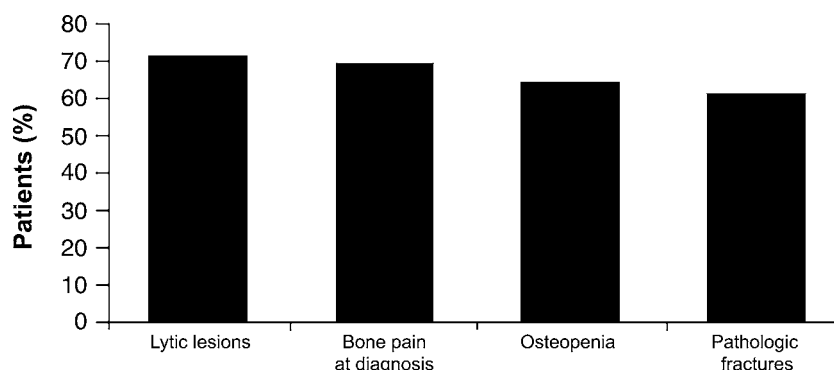
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0093-7754/03/3002-0504\$30.00/0

doi:10.1016/S0093-7754(03)00172-6

Fig 1. Frequency of skeletal abnormalities and bone pain in 842 patients with multiple myeloma seen at the Mayo Clinic from 1960 through 1971. Data from Kyle.²



ized trial involving 392 patients with advanced multiple myeloma (stage III with at least one lytic lesion), intravenous (IV) pamidronate (90 mg every 4 weeks for nine cycles) in addition to anti-myeloma therapy significantly reduced the occurrence of any skeletal events at 9 months (24% *v* 41%; *P* < .001). The benefit was evident in patients receiving both first- and second-line anti-myeloma therapy. However, pamidronate had no effect on overall survival after a median follow-up of 17 months.¹¹

Gallium nitrate is an antiresorptive agent that is highly effective in the treatment of cancer-related hypercalcemia.¹²⁻¹⁵ The drug stabilizes bone crystal¹⁶ and enhances the production of collagen by osteoblasts.¹⁷ Based on these properties, a preliminary randomized pilot study of gallium nitrate was undertaken in patients with multiple myeloma to assess its effects on osteolysis.¹⁸ Patients were randomized to treatment with gallium nitrate for 12 months or to observation only for the first 6 months followed by gallium nitrate treatment in the succeeding 6 months. Gallium nitrate was administered in monthly cycles by subcutaneous injection in dosages of 30 mg/m² daily for 2 weeks followed by a 2-week period with no therapy. The subcutaneous injections were supplemented by a continuous IV infusion at a dose of 100 mg/m² daily for 5 days every other month. Total body calcium was assessed using delayed-gamma neutron activation; bone density was measured by whole-body scanning using dual-photon absorptiometry. A skeletal survey was performed by conventional radiologic techniques and used to calculate a vertebral fracture index.¹⁸

There was a clear trend for increased calcium accretion into the bone among patients receiving

gallium nitrate compared with the observation group, with a mean difference in total body calcium of 3% over the 6-month treatment period (Fig 2). The effect was maintained throughout the 12-month study duration, with a mean change in total body calcium of 7.3% among patients who received the full 12 months of gallium nitrate therapy. In contrast, patients in the observation group tended to have a decrease in total body calcium at 6 months (Fig 2). However, subsequent administration of gallium nitrate to these patients tended to stabilize or improve total body calcium. Regional bone density in the single-most involved site in the observation group showed a median decline of 1.4%, while regional bone density was unchanged in the gallium nitrate-treated patients. Similarly, mean vertebral fracture index decreased by 27% in the observation group compared with a mean decline of 2% in the gallium nitrate group during the first 6 months. Overall, these results were very promising, which provided an early basis for the role of antiresorptive agents, including gallium nitrate, to attenuate both the rate of bone loss and skeletal complications in patients with multiple myeloma.¹⁸

We conducted a retrospective analysis of patients with multiple myeloma who were treated with the M-2 chemotherapy protocol at the Memorial Sloan-Kettering Cancer Center (New York, NY).¹⁹ The M-2 protocol consists of vincristine (0.03 mg/kg IV on day 1), carmustine (BCNU) (0.5 mg/kg IV on day 1), cyclophosphamide (10 mg/kg IV on day 1), melphalan (0.25 mg/kg orally for 4 days or 0.1 mg/kg for 7 to 10 days), and prednisone (10 mg/kg day orally for 7 days, then tapered to zero).²⁰ We identified a common feature shared by a subgroup of patients

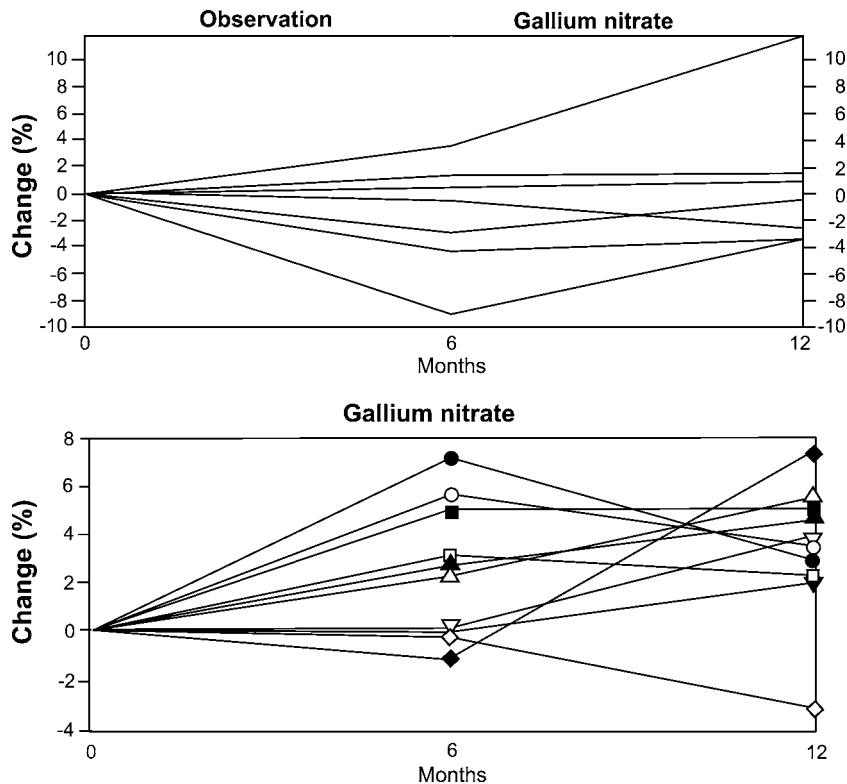


Fig 2. Percent change in total body calcium in patients with multiple myeloma in: (top) patients observed for the first 6 months followed by treatment with gallium nitrate for 6 months and (bottom) after 6 and 12 months in 10 patients maintained on gallium nitrate for 1 year. (Source: Figure 1 from Warrell RP Jr, Lovett D, Dilmanian FA, et al: Low-dose gallium nitrate for prevention of osteolysis in myeloma: results of a pilot randomized study. *J Clin Oncol* 11:2443-2450, 1993. Reprinted with permission of the American Society of Clinical Oncology.¹⁸)

whose survival was quite long: namely, their participation in the pilot randomized study of gallium nitrate.¹⁹ The patients who received gallium nitrate survived for up to 12 years despite an aggressive disease presentation, which far exceeded their expected survival. Consequently, we then further examined the patient groups (M-2 alone *v* M-2 plus gallium nitrate) to determine whether factors other than gallium nitrate therapy may have contributed to the improved outcome.¹⁹

Among the 13 gallium nitrate-treated patients, the disease stage at diagnosis was IA in two patients, IIIA in 10 patients, and IIIB in one patient. Ten patients had IgG paraprotein isotype, two had IgA isotype, and one had lambda light chain isotype. Median values for laboratory parameters were: paraprotein level, 6,000 mg/dL (range, 3058 to 8675 mg/dL); β_2 microglobulin, 2.7 mg/L (range, 1.2 to 9.6 mg/L); hemoglobin, 10.2 g/dL (range, 8.3 to 12.6 g/dL); albumin, 3.7 g/dL (range, 2.5 to 5.0 g/dL); calcium, 10.0 mg/dL (range, 8.3 to 14.5 mg/dL); and lactate dehydrogenase, 166 U/L (range, 142 to 237 U/L). The clinical features of patients who received the M-2 regimen and the

subgroup that also received gallium nitrate are summarized in Table 1. Overall, the patient groups were similar; the only major difference was the longer survival in gallium nitrate-treated patients

Table 1. Clinical Characteristics of Patients Treated With the M-2 Chemotherapy Protocol and the Subset of Patients Who Received M-2 Plus Gallium Nitrate

Characteristic	M-2 (n = 167)	M-2 + Gallium Nitrate (n = 13)
Median age (y)	57	51
Male (%)	60	38
Survival (mos)	48	87+
Response to initial therapy (%)	78	100
Stage III (%)	73	84
IgG and IgA (%)	83	92
Light chain only	17	8
Hb < 8.5 g/dL (%)	16	15

Abbreviations: M-2; vincristine, carmustine, cyclophosphamide, melphalan, prednisone; Hb, hemoglobin.

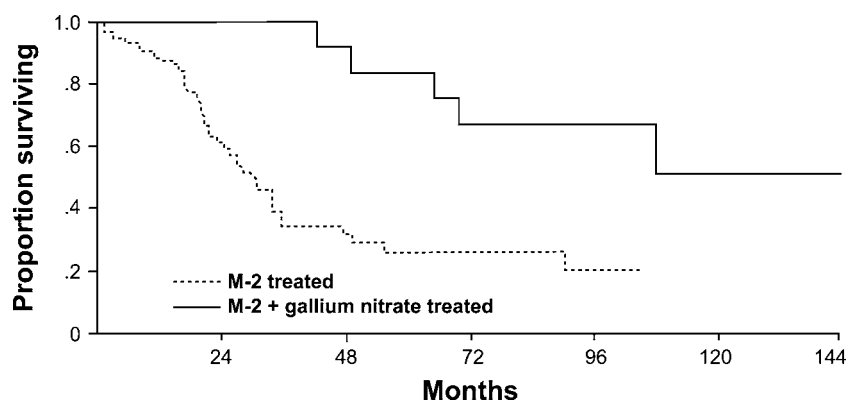


Fig 3. Survival among patients treated with M-2 protocol (n = 167) or M-2 plus gallium nitrate (n = 13). (Reprinted with permission of Taylor & Francis Ltd; <http://www.tandf.co.uk/journals>.¹⁹)

and the higher response to initial treatment. Median survival in the M-2 plus gallium nitrate group was 87+ months compared with 48 months for the group receiving M-2 alone (Fig 3). The M-2 plus gallium nitrate group included two patients with stage III disease who were alive at 137+ and 144+ months. In addition, the patient with stage IIIB disease at presentation in the M-2 plus gallium nitrate group was alive at 96+ months and in complete remission.¹⁹

One possible explanation for the observed difference may relate to the requirement for treatment response before inclusion in the gallium nitrate protocol. Because response to treatment is an important predictor of survival, prolonged survival among the gallium nitrate-treated patients may have been because of a selection bias. However, because there were no long-term survivors among the patients receiving M-2 alone, this is unlikely to be the primary explanation.¹⁹ It is also conceivable that gallium nitrate may positively impact survival by decreasing skeletal complications, via a direct action on the cytokine network involved in promoting proliferation of malignant myeloma cells, or by retarding progression of myeloma by making bone less susceptible to resorption.

FUTURE DIRECTIONS

The promising results produced by gallium nitrate on multiple myeloma-induced osteolysis and on potential disease progression suggest that this agent and its effects on this disease deserve further evaluation. The effects of gallium nitrate on TRANCE, OPG, and osteoclast-activating factor (eg, TNF, IL-6) production should be evaluated in myeloma cell lines. In addition, its effects in the

SCID-hu murine model of myeloma should be evaluated. Clinically, further evaluation of the antiresorption effects of gallium nitrate in patients with multiple myeloma should use typical endpoints, such as the number of skeletal events assessed by magnetic resonance imaging, skeletal survey, and the degree of pain control, but also include evaluation of its effects on markers of bone resorption and formation. Future randomized trials should include an evaluation of the effects of gallium nitrate on bone marrow, plasmacytosis, the expression of TRANCE and OPG, and overall survival. The reintroduction of gallium nitrate provides an opportunity to further study the potential role of this potent antiresorptive compound in the treatment of multiple myeloma.

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