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Intravenous Pamidronate in the Management of Cancer-Associated Hypercalcemia: An Experience in the Taipei Veterans General Hospital

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Key Words
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ABSTRACT

In the management of cancer patients, the metabolic complications of hypercalcemia are commonly encountered. Therapeutic modalities, including adequate hydration, diuretics, steroids, and bisphosphonates, such as pamidronate, are commonly used for the treatment of hypercalcemia. This study is performed in attempt to evaluate the efficacy and toxicity of intravenous pamidronate. In this prospective, phase-II clinical trial, there were overall 18 patients (5 with breast cancer, 3 with multiple myeloma, 2 with malignant lymphoma, 2 with pulmonary squamous cell carcinoma, 2 with hepatocellular carcinoma, and 4 with others) had persistent cancer-related hypercalcemia after 48 h hydration by normal saline. We divided these patients into 3 groups who received different doses (30, 45, and 60 mg) of pamidronate based on the severity of the hypercalcemia. Our results showed that there was one patient died within 2 days after being given pamidronate and it was therefore unable to assess the response in this patient. Fourteen of 17 patients (82.4%) achieved a reduced serum calcium level to normal range within 8 days. The median time for recovery of hypercalcemia was 4 days (range 2 to 7) after treatment. The median duration of sustaining normocalcemia was 18 days (range 5 to 199 days). Of those 14 patients who returned to normocalcemia, 6 (42.9%) experienced hypercalcemia again and 4 underwent the second course of pamidronate treatment, while only 1 achieved normocalcemia. Regarding the side effects of pamidronate, 6 (35.3%) experienced fever, and 13 (76.5%) had asymptomatic hypophosphatemia. Transient lymphopenia and asymptomatic hypocalcemia were also noted without clinical significance. Otherwise, no other significant toxicity was observed. Based on this study, the efficacy and relative low toxicity of pamidronate were beneficial in the treatment of cancer-associated hypercalcemia.

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INTRODUCTION

Hypercalcemia is a common metabolic complication of malignancy which occurs in 5% to 10% of patients with advanced cancers.[1,2] If appropriate medical treatment is not given promptly, patients suffering from hypercalcemia are likely to go rapidly downhill and be exposed to dangerous clinical events. Accurate diagnosis and timely interventions are not the only life saving procedures; appropriate calcium-lowering agents are also necessary for long term survival and are beneficial in improving the life quality.[2]

It has already been demonstrated that giving a combination of fluid-repletion and bisphosphonates is one of the most effective therapies for cancer-associated hypercalcemia.[3,4] Pamidronate (3-amino--1-hydroxy propylidene-1,1-bisphosphonic acid, APD) is a second generation bisphosphonates and in randomized, comparative trials, it was demonstrated that the calcium levels of patients in the pamidronate group regained normocalcemia faster and were able to sustained longer.[3,5,6] To test the efficacy and toxicity of intravenous pamidronate, we performed a prospective, open phase-II clinical trial on patients with cancer-associated hypercalcemia.

PATIENTS AND METHODS

Patients

In total, 18 patients with cancer-associated hypercalcemia of various types were enrolled in this study. Their characteristics are shown in Table 1. Eligibility for this study was based on the following criteria: proven malignant diseases with an elevated serum calcium level (adjusted for serum albumin) of > 10.4 mg/dL persisting after 48 h of hydration with 3 L of normal saline per day. Patients had to be older than 18 years, and signed informed consent before entering to this study. Exclusion criteria included patients undergoing concurrent administration of other medications containing bisphosphonate or any other treatments for hypercalcemia with steroids; patients with severe renal impairment with serum creatinine > 3 mg/dL; patients known to have an allergy to pamidronate or other bisphosphonate; and patients with familial benign hypercalcemia, vitamin D intoxication or hyperparathyroidism. Lactating mothers and pregnant women were also excluded in this study.

Because pamidronate produces a dose-dependent decrease in plasma calcium,[7] patients were allocated into 3 groups with different doses of pamidronate based on the severity of the hypercalcemia at presentation (Table 2).

Methods

Blood samples were collected daily for analysis during the period of 2 days before and 7 days after medication; then the samples were collected once a week in the following 8 weeks. Tests included white blood cell count, differential cell count, hemoglobin, platelets, serum albumin, serum calcium, phosphate, urea, creatinine, and magnesium. Serum calcium level was adjusted according to the serum albumin level by

Table 1. Details of Tumor Type and Bony Metastasis

Tumor type	Bony met (+)	Bony met (-)	Total
breast carcinoma	5	0	5
multiple myeloma	0	3	3
lymphoma	0	2	2
squamous cell lung cancer	2	0	2
hepatocellular carcinoma	0	2	2
renal cell carcinoma	1	0	1
ovarian carcinoma	1	0	1
laryngeal carcinoma	0	1	1
TCC of urinary bladder	1	0	1

met = metastases; TCC = transitional cell carcinoma.

Table 2. Different Doses of Pamidronate Given According to the Severity of Hypercalcemia

Group	No.	Ca (mg/dL)	Ca (mmol/L)	Dose of pamidronate
I	6	10.4-12.0	2.6-3.0	30 mg
II	8	12.1-14.0	3.1-3.5	45 mg
III	4	> 14.1	> 3.6	60 mg

*Adjusted serum calcium level according to fluctuations of the serum albumin level after rehydration.

the following equation:

Corrected calcium (mg/dL) = measured calcium (mg/dL) - albumin (g/dL) + 4

Definitions for Assessing Efficacy

Patients whose serum calcium level decreased below 10.4 mg/dL within 8 days after pamidronate were classified as "responders". Patients who had no change in serum calcium level for 8 days, and the level remained the same for additional 8 days were classified as "non-responders". Patients whose serum calcium decreased for a short period within 8 days, but returned to a hypercalcemic level (above 10.4 mg/dL) were classified as "partial responders elapse" was defined as calcium levels exceeding 10.4 mg/dL twice within 8 weeks after treatment. The duration of normocalcemia was recorded by giving pamidronate to patients who relapsed (adjusted serum calcium > 10.4 mg/dL). Non-responders were excluded from the duration of normocalcemia analysis. Those who developed their first relapse within 8 weeks were allowed to undergo pamidronate therapy again, but those who did not respond or who experienced a second relapse were dropped from the study. Differences in mean values before and after pamidronate treatment were analyzed using Wilcoxon signed rank test, where a p value < 0.05 indicates statistical significance.

RESULTS

One patient died within 2 days of beginning pamidronate treatment owing to progressive malignancy, and no response was assessed. Of the 17 remaining patients, 14 (82.4%) achieved normocalcemia within 8 days and were defined as responders". The other 3 patients failed to respond to pamidronate and retained a high serum calcium level for 8 days after therapy; they were defined as "non-responders". There were no "partial responders" in this study. The median time for lowering hypercalcemia to the normal limit was 4 days (range, 2 to 7 days). The median duration of sustaining normocalcemia was 18 days (range, 5 to 199 days). Fig. 1 shows the change in adjusted serum calcium level after pamidronate treatment. Six patients among

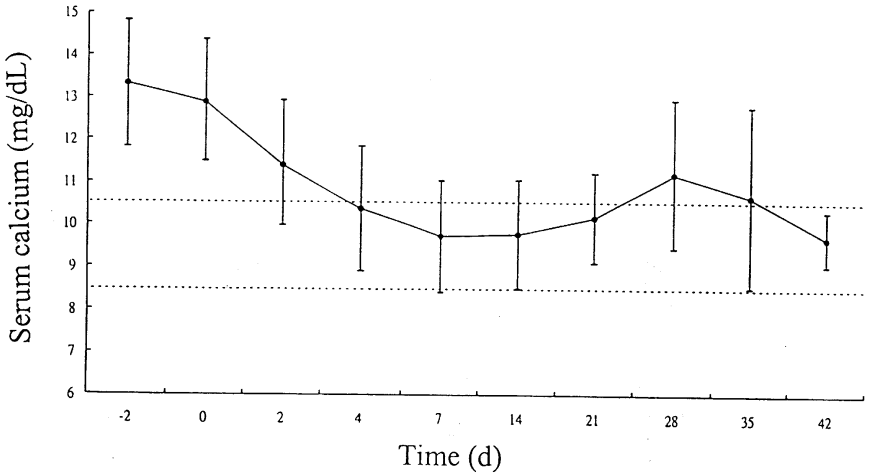

Fig. 1. Serial changes in adjusted serum calcium levels after pamidronate treatment. Points are means; bars are standard deviation; the reference range is indicated by horizontal dotted lines.

the responders (6/14; 42.9%) relapsed and 4 among them underwent second course of pamidronate infusion, but only 1 achieved normocalcemia.

Patients complained of no severe side effects in this study except for fever, transient lymphopenia, asymptomatic hypocalcemia, and hypophosphatemia. Six patients (35.3%) experienced fever during the first 24-48 h after administration of pamidronate. Four of them were treated with acetaminophen. Fig. 2. shows the serial changes in the white cell count. There was a transient but significant decrease ($p = 0.0046$) in the lymphocyte count during the first 7 days after pamidronate treatment, but it was not clinically significant. No significant changes in neutrophil count, hemoglobin level, or platelet count, were found in this study. Transient and asymptomatic slight hypocalcemia (with a range between 7.3 and 8.2 mg/dL) was observed in 3 patients, but they recovered spontaneously within days. Fig. 3 shows the serial changes in serum phosphate levels. There was a significant fall in serum phosphate level over 13 patients (76.5%), but all were asymptomatic; and no other particular laboratory ab-

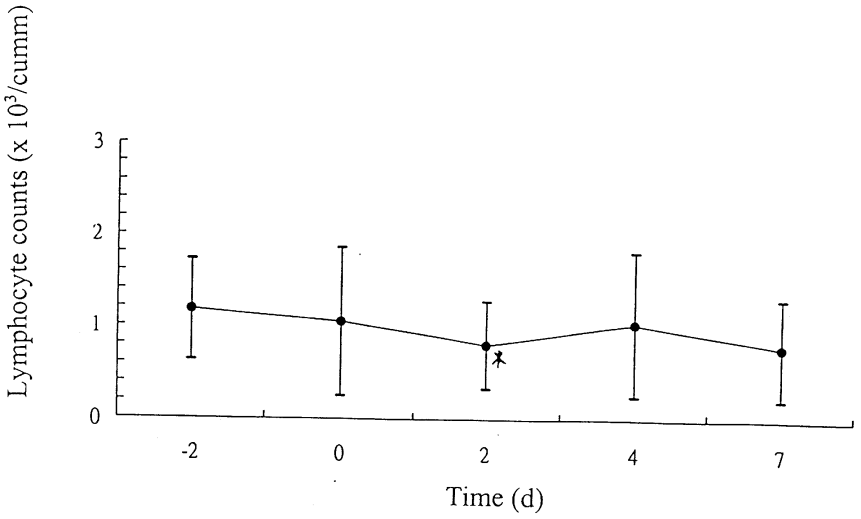

Fig. 2. Lymphocyte counts following pamidronate treatment. Points are means; bars are standard deviation. *$p<0.05$.

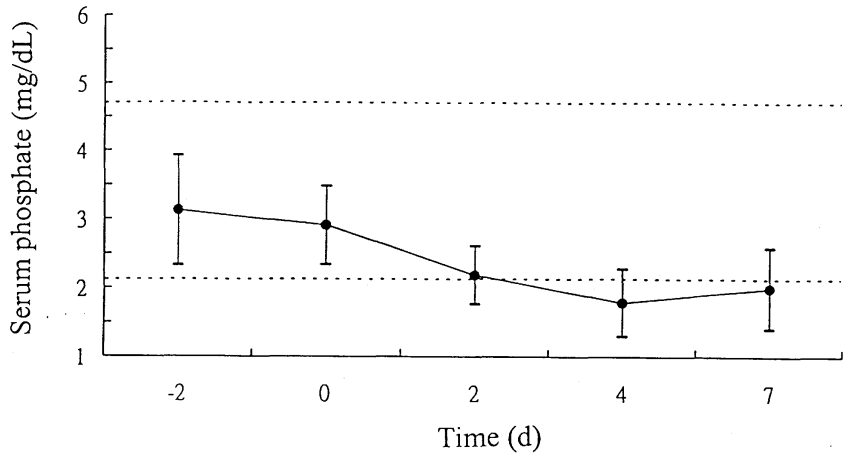

Fig. 3. Serial changes in serum phosphate levels following pamidronate treatment. Points are means;bars are standard deviation; the reference range is indicated by the horizontal dotted lines.

nor mal i ties were found in this study.

DISCUSSION

Bisphosphonates are struc tural an a logues of pyrophosphate, a nat u rally oc cur ring com po nent of crys tal-line bone. Regarding bones, bisphosphonate alters both the struc ture and func tion of os teo clasts, so it may inhibit the phenomenon of osteolysis.[8] Pamidronate, the sec ond gen er a tion bisphosphonate, has emerged as an effective agent for the treatment of can cer-associated hypercalcemia in re cent years.[3,9] It not only acts di rectly on os teo clasts by its poi son ing ef fects but also inhibits their activity. There is evidence that it may have the abil ity to im pair the re cruit ment of monocyte precursors and maturation of osteoclasts.[6,8] Initially, can cer-associated hypercalcemia was treated by ways other than through an in tra ve nous route.[10] How ever, it is now available for an intravenous infusion drug which is much more rapid and more ef fec tive in the active re mod el ing of bones,[8] by com par ing to the poor intes ti nal ab sorp tion of bisphosphonates.[10]

We di vided the pa tients into 3 groups with dif fer ent dos ages (30, 45, and 60 mg). Each group was given a single-dose in fu sion over a 4- to 8-h pe riod based on the se ver ity of the hypercalcemia at pre sen ta tion. Previous studies reported that within 3-4 days, around 90% (87.5% to 100%) of patients achieved normocalcemia after being given pamidronate.[3,6,11] The serum cal cium lev els re mained within nor mal lim its for a median of about 3 weeks, which is longer than that achieved with etidronate.[3,5,6,12] In our study, most patients (82.4%) achieved prolonged normocalcemia with a me dian normocalcemic du ra tion of 18 days. The me dian time for at tain ing normocalcemia was 4 days. The re sults are al most com pat i ble with those authors of Body et al.[12] Re lapse of hypercalcemia was 42.9% in our re spond ers. When a sec ond course of pamidronate was given, only 1 pa tient achieved normocalcemia. We suspected that this was due to an insufficient dosage hav ing been ad min is trated in the sec ond course. Some authors recommended that a high dosage (90 to 180 mg) of pamidronate was ef fec tive in the in hi bi tion of bone resorption in hypercalcemic patients, who were re sis tant to a con ven tional dos age of bisphosphonates.[4] Using an es ca lated dos age of pamidronate for re lapsed hypercalcemia needs fur ther dis cus sion and re search.

Bisphosphonates appear to be less effective in some pa tients with ma lig nancy re lated hypercalcemia owing to high serum level of parathyroid hormone-related protein (PTH-rp).[2,13,14] In our study, 3 non-responders were revealed to have this phenomenon. However, we lacked the necessary laboratory data to sup port this find ing.

In conclusion, most patients experienced sig nif i-cant improvements after being given pamidronate in our study . This re sult sup ports the view point that in tra-ve nous pamidronate pro vides a use ful pal lia tive ther a-peu tic mo dal ity in im prov ing qual ity of life of ter mi nal can cer pa tients.

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