ISSN 0025-7680

SPECIAL ARTICLE MEDICINA (Buenos Aires) 1997; 57 (Supl. I): 109-113

ORAL PAMIDRONATE IN THE PREVENTION AND TREATMENT OF SKELETAL METASTASES IN PATIENTS WITH BREAST CANCER

ANGELIQUE T.M. VAN HOLTEN-VERZANTVOORT[1], SOCRATES E. PAPAPOULOS[2]

Comprehensive Cancer Center, Amsterdam[1] and Department of Endocrinology and Metabolic Diseases, University of Leiden Medical Center[2], The Netherlands

Summary Bone metastases are common in patients with breast cancer and cause considerable morbidity and deterioration of the quality of life. The main pathogenetic mechanism is stimulation of osteoclastic bone resorption by factors produced by the cancer cells. Pamidronate given intravenously suppresses bone resorption and is an effective treatment of malignancy-associated hypercalcemia. Recent data indicate that it can also reduce skeletal morbidity in normocalcemic patients with breast cancer and osteolytic metastases. In a series of studies we examined the long-term efficacy of oral pamidronate in the prevention and treatment of skeletal metastases in patients with breast cancer. In patients with bone metastases oral pamidronate given for a median period of about 20 months reduced significantly skeletal morbidity and had a favourable effect on selective aspects of the quality of life of the patients. Treatment did not alter the radiological course of the disease or the overall survival of the patients. In contrast, oral pamidronate given to patients with advanced breast cancer but no demonstrable bone metastases did not prevent or delay the appearance of the first clinical or radiological manifestation of bone metastases. This treatment is therefore very effective in patients with established metastatic bone disease. More studies are needed to define the place of pamidronate (and of other bisphosphonates) in the prevention of bone metastases in patients at risk.

Key words: oral pamidronate, bone metastases, breast cancer

Pathogenesis and morbidity of bone metastases

The skeleton is a common site of distant metastases from cancers of the breast, the prostate, the thyroid, the kidney and the lung. About 70% of the patients with advanced breast cancer have clinically manifest metastatic bone disease and 85% of them at autopsy. Similar incidences have been reported in men with prostate cancer[1]. Bone metastases cause severe morbidity and deterioration of the quality of life. Pain is the dominant complaint occurring in 60-75% of patients. It was estimated that pain due to bone metastases accounts for about 40% of all cancer-related pains. There is, however, no clear correlation between the extent of metastatic bone disease and the severity of bone pain[2]. Pathological fractures occur in up to 30% of patients with bone metastases and affect mainly the proximal femur (50% of the cases) or the humerus (15%). Vertebral fractures may eventually occur in the majority of patients with osteolytic metastases[3]. Vertebral collapse, spinal angulation or dislocation and expansion of the malignant tissue into the epidural space can cause spinal cord compression. Such complications occur in up to 20% of patients with metastases in the spine and spinal cord compression. Such complications occur in up to 20% of patients with metastases in the spine and spinal cord compression is localized more frequently in the thoracic spine[4]. Hypercalcemia occurs in about 10% of patients with bone metastases and indicates excessive and rapidly progressive bone

Postal address: Dr. Socrates Papapoulos, Department of Endocrinology, Building 1, C4-R, University Hospital, Rijnsburgerwer 10, 2333 AA Leiden, The Netherlands.

destruction. Hypercalcemia, however, may also occur in the absence of demonstrable skeletal metastases[5].

Bone metastases are not indicative of terminal stages of the disease and do not cause mortality, unless complicated by hypercalcemia. On the contrary, the disease often runs a protracted clinical course and patients may live long and suffer from the consequences of bone metastases. In breast cancer, for example, the median survival time after first recurrence in the skeleton is 16 to 24 months, extending to several years if the metastases are confined to the skeleton[6]. Thus palliative therapy aiming at reducing skeletal morbidity is essential.

The metastatic process is far from random and involves a complex cascade of events. Metastasis to the skeleton is a selective process and only a limited number of neoplasms metastasize preferentially to bone[7]. The mechanism(s) responsible for this selectivity is not yet known. The malignant cells are seeded in the bone marrow, they increase osteoclastic bone resorption and they invade the bone. The main mechanism responsible for bone destruction is stimulation of the formation and activity of osteoclasts by factors secreted by the tumour cells, leading to increased bone resorption. Some tumours, such as prostate cancer, secrete factors which mainly stimulate bone formation, leading to predominantly osteos-clerotic metastases. The features of osteolytic and osteosclerotic metastases are probably determined by the net balance of tumour-derived factors. Last but not least, systemic tumour-derived humoral factors, such as parathyroid hormone-related protein, can stimulate osteoclastic bone resorption but may also be found in metastatic sites[8,9].

Bisphosphonates in the management of metastatic bone disease

For most cancers there is no cure once metastases develop. Therapy aims at reducing symptoms and maintaining a good quality of life. Palliative care for bone metastases with currently available measures is far from optimal and therapies which effectively control or prevent skeletal morbidity are needed. Because enhanced osteoclastic bone resorption is the main pathogenetic mechanism of the development and progression of bone metastases, antiresorptive agents such as bisphosphonates present an attractive therapeutic option.

In 1979 it was shown for the first time that pamidronate treatment can inhibit tumour-induced osteolysis in normocalcemic patients with bone metastases[10]. Since then a number of studies with pamidronate or other bisphosphonates have addressed this issue. Two principal approaches have been used with pamidronate. The first is with intermittent intravenous infusions and the second with continuous oral administration of the drug. In controlled studies of patients with breast cancer and osteolytic metastases intravenous pamidronate 45 mg every 3 weeks or 90 mg every 4 weeks was shown to reduce significantly the progression of bone metastases as well as skeletal morbidity[11,13]. Our experience with continuous oral administration of pamidronate is summarized in the following paragraphs.

TABLE 1.- *Mean event rate* (total number of events) in 81 pamidronate and 80 control patients*

	Hypercal-cemia	Bone pain	Impending fracture	Systemic therapy	Radio-therapy
pamidronate	0.5 (5)	2.6 (37)	0.5 (9)	4.1 (64)	2.6 (35)
control	1.6 (24)	3.7 (67)	1.0 (20)	6.3 (113)	3.9 (67)
p	*0.003*	*0.004*	*0.02*	*0.005*	*0.002*

* was calculated per patient as the occurrence of events on the basis of 100 months of follow-up

Oral pamidronate in patients with breast cancer and bone metastases

Because breast cancer patients with skeletal metastases may survive long requiring long-term palliative therapy we decided to treat them with oral, rather than with intravenous pamidronate[14]. A final report of this study was published in 1993[15]. One hundred and sixty one patients with breast cancer and bone metastases were randomized to receive pamidronate (81) or were used as controls (80), for a median period of 18 and 21 months, respectively. The dose of pamidronate was 600 mg in the early stage of the study and was reduced to 300 mg/d because of gastrointestinal side effects which were attributed to the drug. Fifty two of the 81 patients received 300 mg/d from the beginning. Decisions about cancer therapy were left to the treating oncologists. Events of skeletal morbidity and related therapies were recorded and bone scans and skeletal radiographs were made. Quality of life was assessed by a questionnaire containing items of 4 domains relating morbidity due to bone metastases or to pamidronate treatment, namely bone pain, mobility impairment fatigue and gastrointestinal side effects.

An intention to treat analysis showed significant reduction of the overall skeletal morbidity in pamidronate-treated patients ($p = 0.02$). Episodes of hypercalcemia, bone pain and symptomatic impending pathological fractures were reduced by 65%, 30% and 50%, respectively. These responses were associated with significant decreases in the need for systemic antitumour therapy and radiotherapy by 35% (Table 1). The number of pathological fractures was also reduced (8 in the pamidronate group, 15 in the control group) but the difference did not reach significance due to the low numbers. It should be noted that the effect of pamidronate on skeletal morbidity started early and was gradual persisting over time. Despite the favourable clinical and biochemical responses to pamidronate therapy, there were no differences in the radiological course of the disease between the two groups. The overall survival was also comparable as might be expected by a treatment which has no direct antitumour effects.

The reduction of the dose of pamidronate early in the study allowed an analysis of dose differences and results suggested a dose-dependent effect on events of skeletal morbidity. The effect of pamidronate treatment on skeletal morbidity was associated with measurable improvement in selective aspects of the quality of life, assessed by a questionnaire[16]. There were significant favourable early responses of bone pain and mobility. There were no differences, however, in the level of fatigue between the groups and, perhaps surprisingly, in the frequency of gastrointestinal complaints. As in the overall analysis these responses were also dose-dependent with better improvements in pain and mobility in patients treated initially with the higher dose.

Pamidronate treatment was associated with gastrointestinal toxicity (mainly nausea and vomiting) leading to withdrawal of 25% of the patients from the trial. However, in the analysis of the quality of life survey the frequency of gastrointestinal complaints was similar in both groups of patients. A detailed analysis suggested that gastrointestinal toxicity was associated more with disease and prognosis-related factors[15, 16]. Thus, although there is primary, dose-dependent, intolerance to oral pamidronate these results indicate that in cancer patients other factors such as concurrent cytotoxic therapy and disease progression should

TABLE 2.- *First events* of skeletal morbidity in 65 pamidronate and 59 control patients with breast cancer without bone metastases*

	Hypercalcemia	Systemic therapy	Radiotherapy	Pathological fracture
pamidronate	2	12	1	0
control	2	8	4	1

* presenting events occurred simultaneously in 1 pamidronate and 3 control patients

be also considered when interpreting gastrointestinal toxicity.

Oral pamidronate in patients with breast cancer without bone metastases

The question which arises from these studies is whether pamidronate treatment given in the bone metastases-free stage of the disease may prevent or delay the development of metastases to the skeleton. We addressed this question in a phase III study of patients with breast cancer with a high risk of bone metastases but no evidence of skeletal involvement at study entry. Patients with locally advanced breast cancer (UICC stage III) or with extraskeletal metastases were included in the study (33 and 91, respectively). These were randomized to a pamidronate or to a control group as in the previous study. It is important to note that in the analysis we focused on the first clinical and radiological manifestation of skeletal involvement. A detailed report of this study was recently published[17].

There were no differences in the number and type of the first event of skeletal morbidity between the pamidronate and the control group. After a median period of observation of 19+ months 14/65 pamidronate patients and 12/59 control patients developed signs of metastatic bone disease (Table 2). The risk of a first event of skeletal morbidity determined by actuarial analysis was also similar between the groups. Radiological evidence (bone scan and/or radiographs) of bone metastases was found in 36% of pamidronate-treated patients and in 27% of the controls. In agreement with these results, the quality of life evaluation failed to reveal differences between the two groups. Thus pamidronate treatment in the dose and mode of administration used in this study, did not prevent or delay the first manifestation of bone metastases in patients with breast cancer at high risk but no demonstrable bone metastases. Apart from the dose which in patients without metastases has probably a wider rather than a selective distribution in the skeleton, other factors may also be contributing to the lack of an effect. For example, it is not known whether the production of factors by the tumour cells or their interactions with surrounding tissues are the same or are acquired during interactions with the bone marrow stroma and the bone matrix. More information on these issues are clearly needed.

In conclusion, long-term therapy with oral pamidronate 300 mg/d reduces significantly skeletal morbidity and improves certain aspects of the quality of life of patients with breast cancer and skeletal metastases. This mode of treatment cannot, however, prevent or delay the first manifestation of bone metastases in patients at risk but no demonstrable skeletal involvement at the start of therapy. This outcome may be improved with more potent compounds, or different modes of administration, but clearly more studies on the interactions of bisphosphonates, breast cancer cells, bone marrow and bone matrix are needed[18, 19].

Acknowledgement: Our studies were supported by the Dutch Cancer Society (CKVO 83/09, 88/02), the Prevention Fund (28-B/141) and the Dutch Organization for Scientific Research (NWO 900-541-191).

Resumen

Uso de pamidronato oral en la prevención y el tratamiento de las metástasis esqueléticas de pacientes con cáncer de mama

Las metástasis óseas son habituales en pacientes con cáncer de mama y causan considerable morbilidad y deterioro de la calidad de vida. El principal mecanismo patogenético es la estimulación de la resorción ósea osteoclástica por factores originados por las células cancerosas. Pamidronato administrado por vía intravenosa suprime la resorción ósea y es un tratamiento efectivo para la hipercalcemia maligna asociada. Datos recientes indican que también puede reducir la morbilidad esquelética en pacientes normocalcémicas con cáncer de mama y metástasis osteolíticas. En una serie de estudios examinamos la eficacia a largo plazo de pamidronato oral en la prevención y tratamiento de metástasis esqueléticas en pacientes con cáncer de mama. En pacientes con metástasis óseas, pamidronato oral administrado por un período medio de alrededor de 20 meses redujo significativamente la morbilidad esquelética y tuvo un efecto favorable sobre aspectos selectivos en la calidad de vida de los pacientes. El tratamiento no alteró el curso radiológico de la afección o la sobrevida general de los pacientes. Por el contrario, pamidronato oral administrado a pacientes con cáncer de mama avanzado pero sin metás-

tasis óseas demostrables, no previno ni demoró la aparición de la primera manifestación clínica o radiológica de metástasis ósea. Este tratamiento es por lo tanto muy efectivo en pacientes con efermedad ósea metastática establecida. Se necesitan más estudios para definir el papel del pamidronato (y de otros bisfosfonatos) en la prevención de metástasis en pacientes de riesgo.

References

1. Sher HI, Yagoda A. Bone metastases: pathogenesis, treatment and rationale for use of resorption inhibitors. *Am J Med* 1987; 82 Suppl. 2a:6-28.
2. Bonica JJ. Control of bone cancer pain. *In:* Garattini S, editor. Bone resorption, metastasis and disphosphonates. New York: Raven, 1985; 137-81.
3. Galasko CSB. The role of the orthopaedic surgeon in the treatment of bone pain. *Cancer Surv* 1988; 7: 103-25.
4. Byrne TN. Spinal cord compression from epidural metastases. *N Engl J Med* 1992; 327: 614-9.
5. Paterson AHG. Bone metastases in breast cancer, prostate cancer and myeloma. *Bone* 1987; 8 Suppl. a: S17-22.
6. Clark GM, Sledge GW, osborne CK, McGuireWL. Survival from first recurrence: Relative importance of prognostic factors in 1015 breast cancer patients. *J Clin Oncol* 1987; 5: 55-61.
7. Liotta LA. Cancer cell invasion and metastasis. *Sci Am* 1992; 266: 34-41.
8. Quinn JMW, Matsumura Y, Tarin D, McGee JOD, Athanasou NA. Cellular and hormonal mechanisms associated with malignant bone resorption. *Lab Invest* 1994; 71: 465-71.
9. Wallach S, Avioli LV, Feinblatt JD. Cytokines and bone metabolism. *Calcif Tissue Int* 1993; 53: 293-6.
10. Van Breukelen FJM, Bijvoet OLM, van Oosterom AT. Inhibition of osteolytic bone lesions by (3-amino-1-hydroxypropylidene)-1,1-bisphosphonate (APD). *Lancet* 1979; 1: 803-5.
11. Hortobagyi GN, Theriault RL, Porter L, Blayney D, Lipton A, Sinoff C, et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. *N Engl J Med* 1996; 335:1785-91.
12. Conte PF, Latreille J, Mauriac L, Calabresi F, Santos R, Campos D, et al. Delay in progression of bone metastases in breast cancer patients treated with intravenous pamidronate: results from a multinational randomized controlled trial. *J Clin Oncol* 1996; 14: 2552-9.
13. Theriault R, Lipton A, Leff R, Gluck S, Stewart J, Costello S, et al. Reduction of skeletal related complications in breast cancer patients with osteolytic bone metastases receiving hormone therapy by monthly pamidronate sodium (Aredia®) infusion. *Proc Am Soc Clin Oncol* 1996; Abstract 112.
14. Van Holten-Verzantvoort At, Bijvoet OLM, Cleton FJ, Hermans J, Kroon HM, Harinck HIJ, et al. Reduced morbidity from skeletal metastases in breast cancer patients during long-term bisphosphonate (APD) treatment. *Lancet* 1987; 2: 983-5.
15. Van Holten-Verzantvoort ATM, Kroon HM, Bijvoet OLM, et al. Palliative pamidronate (APD) treatment in patients with bone metastases from breast cancer. *J Clin Oncol* 1993; 11: 491-8.
16. Van Holten-Verzantvoort ATM, Zwinderman AH, Aaronson NK, et al. The effect of supportive pamidronate treatment on selective aspects of quality of life patients with advanced breast cancer. *Eur J Cancer* 1991; 27: 544-49.
17. Van Holten-Vetzantvoort ATM, Hermans J, Beex LVAM, et al. Does supportive pamidronate treatment prevent or delay the first manifestation of bone metastases in breast cancer patients? *Eur J Cancer* 1996; 32a: 450-4.
18. Papapoulos SE, van Holten-Verzantvoort ATM. Modulation of tumour-induced bone resorption by bisphosphonates. *J Steroid Biochem Mol Biol* 1992; 43: 131-6.
19. Van der Pluijm G, Vloedgraven H, van Beek E, van der Wee-Pals L, Löwik C, Papapoulos S. Bisphosphonates inhibit the adhesion of breast cancer cells to bone matrices in vitro. *J Clin Invest* 1996; 98: 698-705.