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Effect of calcitonin on anastrozole-induced bone pain during aromatase inhibitor therapy for breast cancer

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ABSTRACT. This study aimed to investigate calcitonin as an effective therapy for osteoporosis in patients with bone pain during the anastrozole treatment of breast cancer. Ninety-one patients, who were on anastrozole treatment for breast cancer and also suffered anastrozole-induced bone pain, were randomly divided into two groups: the calcitonin group received salmon calcitonin and Caltrate D, and the control group received Caltrate D. All patients were evaluated by the visual analogue scale (VAS) and underwent the dual energy x-ray absorptiometry test for bone mineral density (BMD), and serum osteocalcin (BGP), alkaline phosphatase (ALP), calcium (Ca), and phosphorus (P) were measured at three months before and after the treatment. Significant differences in serum Ca, P, BGP, and ALP were found in each group between before and after treatment ($P < 0.05$), while no differences between the calcitonin and control groups were found. No difference was observed in femur BMD between the two groups, or between before and after treatment in each group. There was a significant difference in spine BMD between before and after treatment in the control group ($P < 0.05$) but not in the calcitonin group, while no difference was found between the calcitonin and control groups. Futhermore, VAS score significantly declined in each

group after treatment ($P < 0.05$), but much more in the calcitonin group than the control group ($P < 0.05$). Our finding suggests that calcitonin may alleviate bone pain during the anastrozole treatment of breast cancer but has no effect on bone loss during cancer treatment.

Key words: Calcitonin; Bone pain; Anastrozole; Breast cancer; Aromatase inhibitor

INTRODUCTION

Adjuvant therapies are necessary and are of benefit for postoperative breast cancer patients (Cuzick et al., 2010; Jiang et al., 2010; Li et al., 2011). But the benefits of anastrozole in treating breast cancer have been accompanied by additional treatment-related toxicity. Therefore, patients with endocrine cancers have an increased risk of osteoporosis as a complication of cancer treatment (Hoff and Gagel, 2005; Body et al., 2007). Bone loss induced by hormone therapy appears in early breast cancer due to hypoestrogenism, and chemotherapy with resultant ovarian failure may also cause bone loss. Bone loss induced by cancer treatment can cause osteoporosis, decreased bone strength and increased risk of fracture (Cooper, 1997; Body et al., 2007). Bone loss induced by hormone therapy is usually rapid and severe, and associated with menopause in women. Thus, the risk of bone loss in breast cancer patients treated with aromatase inhibitor is at least twice that in healthy postmenopausal women (Hadji, 2009).

Calcitonin is a hormone produced in the thyroid glands. Hypocalcemic action for the inhibition of osteoclastic bone resorption leads to increased calcium and phosphorus in urinary excretion. Natural calcitonin and synthetic calcitonin have been clinically used. Salmon calcitonin is the most powerful and used to control bone pain due to malignant neoplasms (Parfitt, 1999). Salmon calcitonin can cause nausea, vomiting and flushing, unpleasant sensations in taste, tingling in hands, and pain at the site of injection. Some patients also experience an allergic reaction. In addition, salmon calcitonin is immunogenic and may develop antibodies, which can lead to drug resistance to its effects during long-term calcium treatment (Grahame-Smith and Aronson, 2002; Lussier et al., 2004).

Currently, the use of calcitonin for relief of metastatic bone pain is not very common, and there is little information available about its use in anastrozole-induced bone pain during aromatase inhibitor therapy for breast cancer. However, there is strong evidence to support the use of risedronate in reducing the risk of both fractures, vertebral and nonvertebral, in postmenopausal women with osteoporosis and hypercalcemia (Zojer et al., 1999; Tugwell et al., 2003). The aim of this study was to investigate the effect of calcitonin as an effective therapy for osteoporosis in patients with bone pain during anastrozole treatment of breast cancer.

MATERIAL AND METHODS

Patients

Ninety-one breast cancer patients at Peking University People's Hospital, who were under anastrozole treatment for breast cancer and also suffered anastrozole-induced bone pain were enrolled. Full inclusion criteria were as follows: 1) age ≥60 years old, or age <60 years

old and with natural menopause of more than 1 year, or with bilateral oophorectomy; 2) undergoing adjuvant aromatase inhibitor therapy 2-4 weeks after surgery or 2-6 weeks after adjuvant chemotherapy; 3) estrogen receptor ≥10 fmol/mg or tumor cells ≥10% by histochemical detection. This study was conducted in accordance with the Declaration of Helsinki. And the study protocol was approved by the local research ethics committee of Peking University (Protocol Record D5395L00006). Written informed consent was obtained from all participants.

Patients were randomly allocated to one of two groups according to the drug received for three months: the calcitonin group received 200 IU/day salmon calcitonin and 600 mg/day Caltrate D, and the control group received 600 mg/day Caltrate D.

Visual analogue scale

Pain level in patients was evaluated with a visual analog scale (VAS) of 0-10 three months before and after the treatment, where 0 was minimal and 10 was maximal pain.

Dual energy x-ray absorptiometry

Patients underwent the dual energy x-ray absorptiometry (DEXA) test for bone mineral density (BMD) three months before and after the treatment. BMD of spine and femur was determined by DEXA (DPXL/PED, Lunar Corp., Madison, WI, USA) according to the manufacturer standard spine and femur protocols.

Biochemistry parameters measurements

Serum osteocalcin (BGP), alkaline phosphatase (ALP), serum calcium (Ca) and phosphorus (P) were also measured in patients three months before and after the treatment. BGP was measured by an EASIA kit (DRG Instruments GmbH, Marburg, Germany). A colorimetric assay kit (BioMerieux SA, France) was used to determine ALP activity as previously described (Belfield and Goldberg, 1971). Serum calcium and phosphorus were measured by atomic absorption spectroscopy.

Statistical analysis

The data are reported as means ± SD. Comparisons between groups of data were performed by the Wilcoxon test, while the Student *t*-test was used for within group comparisons. $P < 0.05$ was considered to be statistically significant. Data were analyzed with SAS9.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

General data

Nine patients were excluded from the study, three in the calcitonin group and six in the control group. Only 82 cases were analyzed. Basic characteristics of study population are shown in Table 1.

Table 1. Basic characteristics of study population.

	Control group (N = 40)	Calcitonin group (N = 42)	P
Age (years)	61.3 ± 6.9	59.6 ± 9.2	0.357
Cancer stage			0.8230
T1N0M0	17 (42.50%)	22 (52.38%)	
T1N0M1	0 (0.00%)	1 (2.38%)	
T1N1M0	8 (20.00%)	7 (16.67%)	
T1N2M0	1 (2.50%)	0 (0.00%)	
T2N0M0	10 (25.00%)	8 (19.05%)	
T2N1M0	4 (10.00%)	3 (7.14%)	
T3N0M0	0 (0.00%)	1 (2.38%)	
Chemotherapy			
None	24 (60.00)	26 (61.90)	0.860
Design			0.129
AC	9 (22.50)	3 (7.14)	
CAF	3 (7.50)	4 (9.52)	
TA	9 (22.50)	18 (42.86)	
TAC	3 (7.50)	1 (2.38)	
Chronic illness			0.6558
Hypertension	3 (7.50%)	3 (7.14%)	
Cerebral infarction	1 (2.50%)	0 (0.00%)	
Diabetes	4 (10.00%)	2 (4.76%)	
None	32 (80.00%)	37 (88.10%)	
Serum calcium	2.29 ± 0.10	2.31 ± 0.12	0.402
Serum phosphorus	1.26 ± 0.18	1.25 ± 0.16	0.817
Serum osteocalcin	12.33 ± 5.08	15.26 ± 9.98	0.100
Alkaline phosphatase	4.37 ± 0.92	4.95 ± 2.58	0.182
VAS	4.48 ± 1.48	5.38 ± 1.40	0.006
BMD-spine	-1.11 ± 1.03	-1.02 ± 1.02	0.717
BMD-femur	-0.92 ± 0.77	-1.17 ± 0.82	0.160
Time of pain onset	12.2 ± 5.9	10.9 ± 4.4	0.238

T1, T2 and T3 = tumor diameter <2, 2-5 and >5 cm, respectively; N0, N1 and N2 = no axillary lymph node metastasis, axillary lymph node metastasis and axillary lymph node metastasis with fusion, respectively; M0 = no distant metastasis; M1 = distant metastasis; AC = adriamycin+cyclophosphamide; CAF = cyclophosphamide+adri amycin+fluorouracil; TA = taxinol+adriamycin; TAC = taxinol+adriamycin+cyclophosphamide.

Changes in the biochemistry parameters

As shown in Table 2, levels of serum Ca, P, BGP and ALP significantly decreased after aromatase inhibitor therapy in both calcitonin and control groups ($P < 0.05$). However, no significant differences in levels of serum Ca, P, BGP, and ALP were observed after aromatase inhibitor therapy between the calcitonin and control groups.

Table 2. Comparison of biochemistry parameters between control and calcitonin group after therapy.

	Before therapy	After therapy	Difference value	In group		Between groups	
				Statistics	P	Statistics	P
Serum calcium						0.0246	0.8758
Control	2.29 ± 0.10	2.25 ± 0.10	-0.04 ± 0.12	2.2987	0.0270		
Calcitonin	2.31 ± 0.12	2.27 ± 0.08	-0.04 ± 0.12	2.0863	0.0432		
Serum phosphorus						0.4323	0.5128
Control	1.24 (1.10-1.34)	1.22 (1.14-1.32)	-1.06 ± 0.14	47.2093	0.0000		
Calcitonin	1.25 (1.14-1.36)	1.23 (1.16-1.29)	-1.08 ± 0.17	40.3782	0.0000		
Serum osteocalcin						0.0974	0.9224
Control	12.36 (8.42-15.02)	11.90 (8.64-18.78)	9.70 (6.23-16.51)	409.0000	0.0000		
Calcitonin	12.51 (6.73-20.56)	10.96 (7.38-18.44)	8.69 (5.16-15.97)	451.5000	0.0000		
Alkaline phosphatase						0.4499	0.6528
Control	4.37 (3.78-5.13)	4.33 (3.46-5.11)	2.04 (1.12-2.92)	409.0000	0.0000		
Calcitonin	4.57 (3.45-5.75)	4.40 (3.23-5.12)	2.02 (1.06-2.75)	444.5000	0.0000		

Changes in BMD

As shown in Table 3, spine BMD significantly decreased after therapy within the control group ($P < 0.01$), but there was no change in the calcitonin group. A significant difference in spine BMD was observed after therapy between the control and calcitonin groups ($P < 0.05$). Furthermore, no statistical differences in femur BMD were found after therapy within or between the two groups.

Table 3. Comparison of bone mineral density (BMD) between control and calcitonin group.

	Before therapy	After therapy	Difference value	In group		Between groups	
				Statistics	P	Statistics	P
BMD-spine						2.0562	0.0398
Control	-1.15 (-1.95-0.45)	-1.25 (-2.20-0.80)	-0.10 (-0.35-0.10)	156.0000	0.0057		
Calcitonin	-1.10 (-1.90-0.30)	-1.30 (-1.80-0.20)	0.00 (-0.20-0.20)	15.0000	0.8019		
BMD-femur						0.0020	0.9641
Control	-0.92 ± 0.77	-0.91 ± 0.75	0.01 ± 0.47	0.0672	0.9468		
Calcitonin	-1.17 ± 0.82	-1.17 ± 0.90	-0.00 ± 0.53	0.0000	1.0000		

Changes in VAS

As shown in Table 4, the VAS score was significantly decreased after therapy within both the control and calcitonin groups ($P < 0.01$). A significant difference in VAS was also observed after therapy between the control and calcitonin groups ($P < 0.01$).

Table 4. Comparison of visual analogue scale (VAS) between control and calcitonin group.

	Before therapy	After therapy	Difference value	In group		Between groups	
				Statistics	P	Statistics	P
VAS						5.6286	0.0000
Control	4.00 (3.50-5.00)	4.00 (1.00-8.00)	-1.00 (-1.50-0.00)	129.0000	0.0013		
Calcitonin	5.00 (5.00-6.00)	2.00 (0.00-7.00)	-3.00 (-4.00 - -2.00)	440.5000	0.0000		

DISCUSSION

This study included the trial involving a total of 91 patients who were treated for anastrozole-induced bone pain with a dose of 200 IU calcitonin per day or placebo. Due to its effects by inhibiting the absorption of osteoclasts and its analgesic activity, it has been hypothesized that calcitonin could be beneficial in treating bone pain, but there is no evidence for the treatment of bone loss.

Calcitonin is found in several species, but that from the salmon is the most widely used because of the characteristics that make it highly potent, namely long half-life, resistance to degradation in plasma and high affinity to specific receptors (Berne and Levy, 1990; Reginster, 1991; Siligardi et al., 1994).

The bone repair is activated by growth hormones and thyroid and parathyroid hormones, and inhibited by calcitonin and cortisone. A temporary interruption of blood with the combination of devitalized bone and tissue necrosis causes the activation of bone repair (Hollinger and Wong, 1996). It is believed that this regeneration occurs based on two combined

mechanisms: induction of proliferation and differentiation of undifferentiated mesenchymal cells, and the induction of osteoprogenitor cell proliferation. One of the most common consequences of hormone loss is osteoporosis due to estrogen deficiency and pathology. Osteoporosis is currently defined as a systemic skeletal disease characterized by low bone mass with impaired tissue microstructure. Osteoporosis is the consequence of a breakdown in bone metabolism characterized by a progressive pathological bone resorption, accompanied by a reduced osteogenesis. This low bone mass is attributed to estrogen deficiency, and decreased bone density with age can be explained at least partly by increased secretion of parathyroid hormone resulting from vitamin D deficiency and low calcium absorption (Young et al., 1987).

Calcitonin is a hypocalcemic thyroid hormone, secreted in the parafollicular cells of the thyroid gland of mammals and actively participates in skeletal homeostasis, as it normalizes the concentration of calcium ions in the plasma. It is a single chain peptide, and its biosynthesis and secretion is regulated by calcium concentration in plasma (Copp et al., 1962). Hypocalcemic and hypophosphatemic effects of calcitonin are caused predominantly by direct inhibition of osteoclastic bone resorption and influence on renal function (Reginster et al., 1992). However, no statistical improvement of BMD in patients was found with calcitonin treatment during anastrozole treatment of breast cancer (Table 3).

Pain relief should be the first target in the treatment of bone pain during anastrozole treatment of breast cancer to improve patients' quality of life. There are different levels of treatment for the relief of pain, which usually begin with an analgesic or nonsteroidal anti-inflammatory drug, and continues with low potency opioids (codeine), and then with other more potent opioids (morphine). However, this drug sequence fails for a variety of reasons, because the medications are not prescribed at higher therapeutic doses. Radiation therapy is commonly used to provide relief from localized painful bone metastases (Hoskin, 1995). About 75% of patients achieve pain relief, and half of them remain free of pain (Jacox et al., 1994). However, in the event of multiple bone metastases, systemic treatments such as bisphosphonates or calcitonin may be necessary for efficacy. Our finding showed that VAS score significantly decreased after therapy in the calcitonin group compared with control group ($P < 0.01$), shown in Table 4. Similar results have been obtained showing efficacy in trials of calcitonin with cancer bone pain management in patients (Wong and Wiffen, 2002).

In summary, our findings suggest that calcitonin can alleviate bone pain during anastrozole treatment of breast cancer but has no effect on bone loss during cancer treatment.

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