BISPHOSPHONATE AND LOW-DOSE DEXAMETHASONE TREATMENT FOR PATIENTS WITH HORMONE-REFRACTORY PROSTATE CANCER

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We evaluated the effects of bisphosphonate (BP) treatment in five patients with hormone-refractory prostate cancer (HRPC), experiencing bone pain from metastases to the bone, and assessed changes in serum prostate specific antigen (PSA) levels, bone pain, and quality of life (QOL). Treatment with incadronate disodium (10 mg) in saline was administered at 2-week intervals for a total of 6 times. Evaluation of the treatment included the incidence of adverse events, QOL, bone pain, pain scale, and blood analyses including tumor markers. BP treatment was generally well tolerated by all five patients. The effects of BP treatment on serum PSA values were evaluated as prominent response (PR), no change (NC) and progressive disease (PD) in one, two and two cases of PD, respectively. During BP treatment, serum type I procollagen values decreased in patients, but there was no large change in serum type I collagen values. Only one patient experienced increased pain ; pain was well controlled in the others. The QOL evaluation by Short-Form 36 (SF-36), showed no change in scores during BP treatment except for general health. These results suggested that BP treatment is safe and feasible. It may be effective for the treatment of those HRPC patients with bone pain and may become one of the choices for treatment of HRPC.

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Key words : Hormone-refractory prostate cancer, Bisphosphonate, Short Form-36, Prostate specific antigen

INTRODUCTION

Prostate cancer (PCa) is one of the most common cancers affecting men in Western countries[1]. The incidence in Japan has been steadily rising during the past few years. In spite of the increasing number of men being examined for prostate-specific antigen (PSA), 30% of the patients with PCa are diagnosed as having advanced cancers with distant metastasis. Endocrine therapy is still a powerful treatment for patients with advanced PCa. Approximately 80% of the patients respond well to this treatment ; but PCa recurs in a hormone-refractory status within two or three years of treatment, in spite of low endogenous androgen levels. Various symptoms such as anemia, bone pain, and compression fracture are often observed due to PCa metastases to bone[2]. Bone pain would be a significant symptom affecting the management of hormone-refractory PCa (HRPC), and the patient's quality of life (QOL) is extremely disturbed. Therefore, delay or prevention of skeletal complications is an important and meaningful clinical benefit for patients with PCa and bone metastases[3]. Bisphosphonate (BP) is a specific inhibitor of osteoclasts and has been widely used as a beneficial agent for the treatment of bone metastases in patients with various types of cancers[4,5]. BP also inhibits cancer cell invasion[6,7] and angiogenesis[8]. It is well recognized that BP reduces osteolysis by promoting apoptosis in osteoclasts[9,10].

We administered BP for treatment of the patients with HRPC having pain due to PCa bone metastases and evaluated the QOL status during the BP treatment.

MATERIALS AND METHODS

Five patients with HRPC treated at Chiba University Hospital between September, 2001 to October, 2002 were entered in this study. Patients' characteristics are shown in Table 1. All patients initially responded to hormone therapy and showed a steady increase in serum prostate specific antigen (PSA). Then we discontinued the antiandrogen and evaluated the patient for the antiandrogen withdrawal syndrome (AWS). An alternative antiandrogen was administered, but the disease was progressive despite castrate levels of serum testosterone[11]. All patients with performance status (PS) of 0 to 2 were expected to have at least 12 weeks of survival. Written informed consent was obtained from all patients. These five patients were treated with low-dose dexamethasone (0.5 mg/day) and LH-RH agonist during BP treatment and had bone pain due to PCa

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Table 1. Patient characteristics at BP treatment

Case	Age	PSA (ng/ml)	Stage*	Tumor* grade	EOD*	Primary treatment
1	68	856	D2	poor	4	LH-RH+AA
2	70	28	C	poor	0	RT+AA
3	55	1,310	D2	mod	3	LH-RH+AA
4	67	63	D2	mod	1	LH-RH+estrogen
5	57	696	D2	mod	2	castration+AA

LH-RH : LH-RH agonist, AA : anti-androgen, RT : radiation therapy, BP : bisphosphonate, poor : poorly differentiated, mod : moderately differentiated, * : patient status of untreated prostate cancer.

metastases to bone. One patient having lumber pain by bone metastases was given palliative radiation therapy for symptom relaxation before BP treatment.

Patients were assigned to a treatment regimen of intravenous BP (incadronate disodium 10 mg in 500 ml saline) administration every 2 weeks for 3 months (total 6 times). Other BPs were not used on these patients. The use of analgesics for osteocopic improvement was allowed.

The response to BP treatment was evaluated as follows. Bone pain in each patient was assessed on a 10-point visual analogue scale (VAS) and global assessments every 2 weeks[12]. For the narcotic scale, usage of pain-killer was also evaluated every 2 weeks. Carboxyterminal propeptide of type I procollagen (PICP) and the pyridinoline cross-linked carboxy-terminal telopeptide of type I collagen (ICTP) were used as bone metabolism markers every 4 weeks. PSA was measured and regular blood tests conducted every 4 weeks. Adverse events such as, fever up, and transient severe bone pain were also recorded. QOL was estimated using a self-answering questionnaire of Short Form (SF)-36[13,14]. The SF-36 consisted of 36 items, aggregated into eight multi-item scales that measured physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The range of scores for the SF-36 subscales was 0 to 100, with a higher score reflecting better health and well-being (e.g., higher bodily pain score means less self-reported pain). The eight scales also were scored to produce two summary measures of physical (physical component summary) and mental health (mental component summary).

The pain response (i.e., pain score and narcotic score) was evaluated as the primary endpoint of BP treatment. Secondary endpoints included, PSA response, time to progression, impact on QOL, changes in markers of bone turnover, and tolerability of the drug combination.

Results of SF-36 scores were compared using a chi-square test, with $P<0.05$ as significant.

RESULTS

As shown in Fig. 1A, only one patient (case 1) showed increase of pain scale value. The other four patients did not show large changes in bodily pain during BP treatment with the use of analgesics. Narcotic scores in all five patients were stable during BP treatment (Fig. 1B). Table 2 shows the scores for each question. As the result of QOL evaluation by SF-36, the QOL scores were not changed during BP treatment except general health ($p=0.0207$).

The effects of BP treatment on serum PSA value were prominent response (PR) in one patient (case 1), no change (NC) in 2 patients (cases 2, 5), and progressive

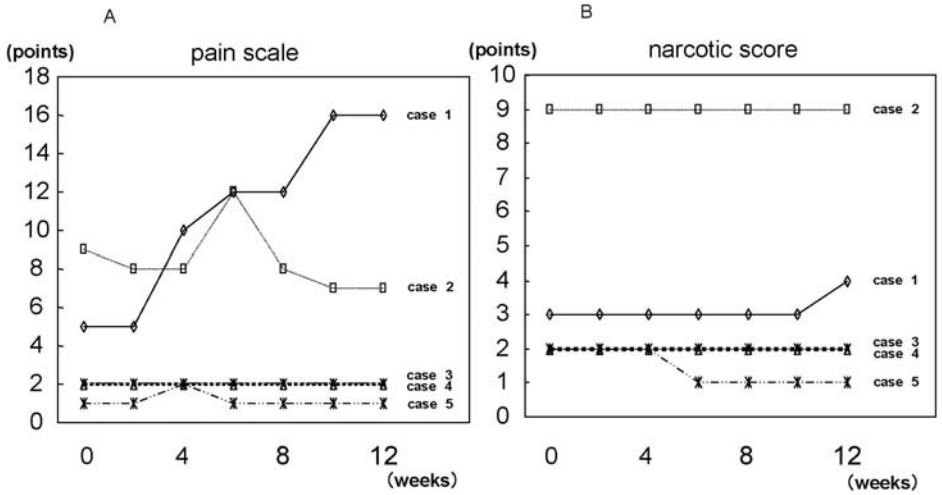


Fig. 1. Changes in pain scale and narcotic scale during BP treatment. HRPC patients having bone pain were treated with incadronate disodium and the changes on the pain scale (1A) and narcotic scale (1B) were evaluated before and after treatment.

Table 2. SF-36 scores in patients with hormone-refractory prostate cancer treated by bisphosphonate and low-dose dexamethasone

Scales of SF-36	Pre-BP treatment (n=5)	Post-BP treatment (n=5)	t test P value
Physical functioning	49±24	33±30	n.s.
Role-physical	75±43	57±49	n.s.
Bodily pain	37±18	35±21	n.s.
General health	46±11	32±13	0.0207
Vitality	46±22	50±22	n.s.
Social functioning	53±32	45±38	n.s.
Role-emotional	73±43	53±51	n.s.
Mental health	50±22	49±24	n.s.

disease (PD) in 2 patients (cases 3, 4) at 12 weeks of BP treatment (Fig. 2). However, when we observed the clinical course after BP treatment, inhibition of PSA rising was present in cases 1, 3, and 5 after six months (Fig. 2A, 2B). During BP treatment, serum PICP value decreased in 4 occasions (Fig, 3A) and a large change was not seen in serum ICTP value (Fig. 3B). As for both serum calcium and alkaline phosphatase values, changes within the normal range were seen in all five patients. Serum I-P value was increased in one patient during BP treatment, but 12 weeks later it was normalized (data not shown). BP treatment was generally well tolerated by all five patients. As for adverse events, transient bone pain progressed and constipation was present in one patient after administration in 12 weeks, but recovered immediately.

DISCUSSION

For the management of advanced PCa, endocrine therapy by androgen ablation is generally effective as an initial treatment. Although the majority of prostate tumors regress after androgen ablation, disease progression inevitably recurs. Successful management of pain in the patients with bone metastases decreases morbidity, improves patient satisfaction, and is an essential component of critical care. Irradiation is effective to reduce local bone pain. However, it is difficult to control recurrent pain after irradiation and pain due to multiple bone metastases. In such cases, BP treatment is a candidate therapy for pain control.

Recent reports suggest that growth of treatment-resistant tumors still depends on maintenance of androgen receptor (AR) signaling pathways. One mechanism proposed for the maintenance of AR signaling in HRPC is ligand-independent activation of the AR by cytokines involving Ras/mitogen-activated protein kinases, Janus-activated kinase (JAK)/signal transducers and activators of transcription, and/or phosphatidylinositol 3′-kinase/Akt[15–17] . However, when progression occurs after initial treatment, changes of anti-androgen, use of steroid, or use of anticancer

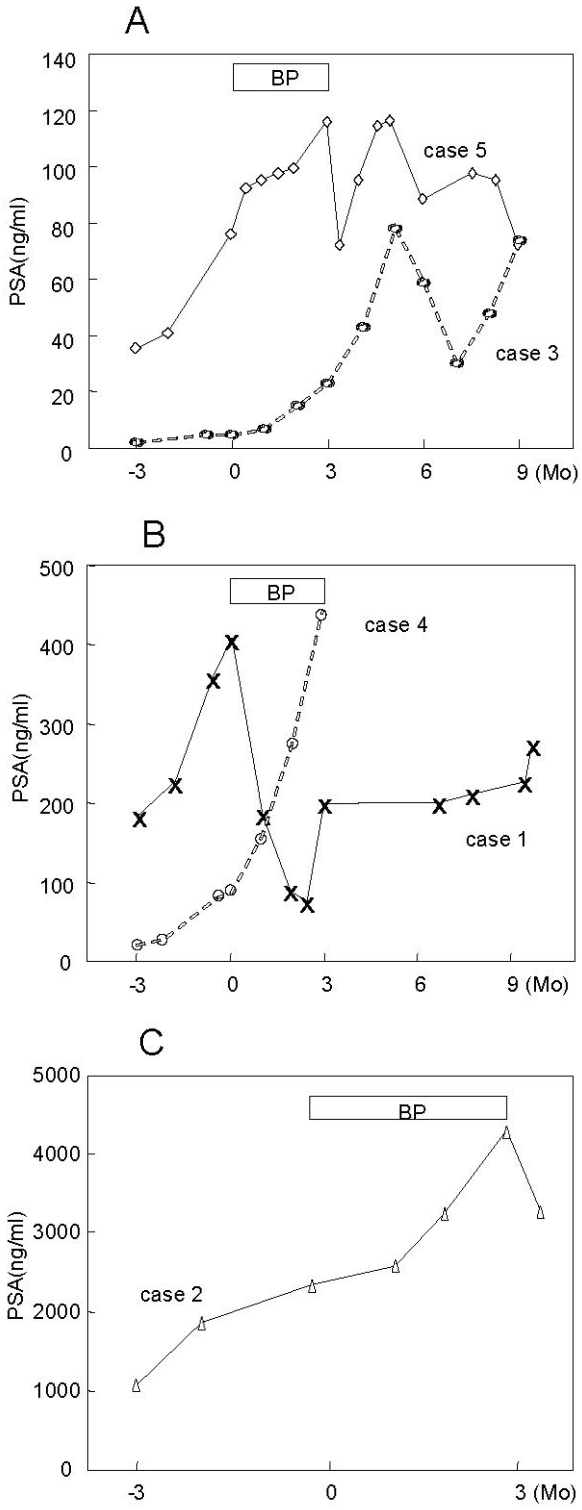
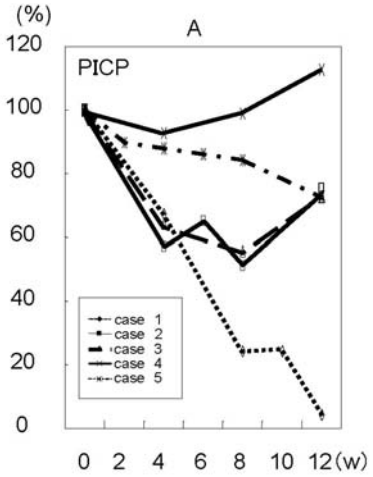


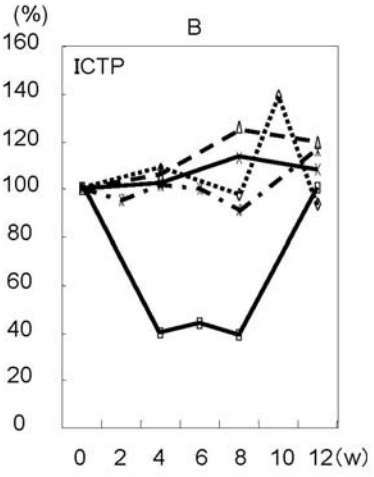
Fig. 2. Changes in serum PSA value during BP treatment. HRPC patients having bone pain were treated with incadronate disodium (10 mg) in 500 ml saline d.i.v. at 2-week intervals (total 6 times). The serum PSA levels before, during, and after BP treatment are shown. A box in BP in each figure indicates the period of BP treatment. (A) ; case 3 and 5, (B) ; case 1 and 4, (C) : case 2.

agents should be considered[18,19]. The effects of these treatments are often temporary, and not long-term.



	0	12 w
Case 1	1,940	76
Case 2	378	284
Case 3	160	116
Case 4	166	188
Case 5	109	116

(ng/ml)



	0	12 w
Case 1	12.4	11.6
Case 2	52.5	52.5
Case 3	4.6	5.5
Case 4	6.1	6.6
Case 5	4.3	5.0

(ng/ml)

Fig. 3. Changes in serum PICP and ICTP during BP treatment. HRPC patients having bone pain were treated with incadronate disodium and the changes in serum PICP (3A) and ICTP (3B) values evaluated.

With progression of the disease, bone pain due to metastasis of PCa cells greatly worsens the QOL of the patients. Various factors such as PSA, uPA, catepsin, PTHrP, PDGF-BB, interleukin-6 are secreted from PCa cells in bone tissue and act on osteroblasts[20,21]. Then osteoblasts induce undifferentiated cells to form osteoclasts. BP inhibits osteoclast formation directly as well as indirectly by modulating signaling from osteoblasts to ostelclasts. BPs decrease bone resorption and can cause a rapid decline in bone resorption markers, the magnitude of which correlates with efficacy in improving pain[22,23].

The first generation bisphosphonates, etidoronate and clodronate, which contain simple substituents lacking a nitrogen atom, become available for clinical use almost 3 decades ago. The second to third generation BPs, such as parmidronate, alendronate, ibandronate, risedronnate, minodronate, and zoledronic acid, have either an aliphatic or a heterocyclic side chain containing one or two nitrogen atoms (nitrogen-containing BPs). Incadronate disodium, one of the third-generation BPs, is a more potent inhibitor of bone resorption (almost 100–1,000 times) in comparison with the first-generation BP etidoronate[24,25]. In a recent study, patients with HRPC and a history of bone metastases were randomly assigned to a double-blind treatment regimen of intravenous zoledronic acid or placebo. Bone pain and analgesic scores decreased more in patients who received zoledronic acid than in patients who received placebo, but there were no differences in disease progression, performance status, or quality-of-life scores among the groups[3]. Moreover, Saad F et al. reported long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic HRPC. Zoledronic acid reduced the incidence of skeletal-related events in men with hormone-refractory metastatic prostate cancer[26]. From such a point of view, early BP treatment might be desirable for the PCa patients with bone metastasis (i.e., stage D2).

BPs also appear to have direct antitumor effects in PCa cell lines. For example, drugs such as zoledronate, clodronate, and alendronate diminish the adhesion and invasiveness of PC3 PCa cells[7]. Asahi H et al. reported that a patient with HRPC in which serum PSA and bone pain were decreased[4]. In our study, serum PSA level was decreased by this treatment in one patient. In addition, when we observed the clinical course after BP treatment, inhibition of PSA rising was present in case 1, 3, and 5 after six months (Fig. 3).

Type I collagen is synthesed by osteoblasts and accounts for about 90% of the organic matrix of bone. ICTP is the degraded form of the type I collagen cross-link. During the formation of type I collagen, PICP is cleaved from procollagen molecules. Both the formation and degradation of type I collagen is a good indicator of bone status and examining them will enable monitoring of the direction and speed of the metabolic turnover of bone[27]. Therefore, PICP and ICTP thus reflect the metastatic burden in bone and are useful for monitoring the response of bone metastasis to therapy[28]. A fall of serum PICP value was observed among bone metabolism markers so that action of osteroclast was expected to be usually restrained in BP treatment.

However, the serum ICTP value was not demonstrated to decrease in this study. This was considered to be due to dexamethasone therapy in all patients. Activity of cytokine including IL-6 was inhibited in metastases to bone lesion by dexamethasone, and, as a result, the bone metabolism marker was not affected[19]. According to analysis of QOL data and pain scale in the HRPC patients treated with BP, the QOL scores during BP treatment did not change except for general health (Table 2). This result may be based on disease progression of PCa.

As for pain scale, improvement was seen in one patient. The absolute number of responders to BP treatment was small. Cases 3, 4 and 5 had a low pain scale and narcotic score before BP treatment. However, as shown in Fig. 2, the speed of PSA rising in these patients suddenly increased during BP treatment. Akakura et al. showed that the speed of increase in PSA is related to the degree of pain in the patients with PCa. Therefore, we consider it to be a better choice of treatment for HRPC[29].

In summary, five patients with HRPC having bone pain were treated with BP. Here we showed that BP treatment is safe and feasible, and may be effective for pain control of the patients with HRPC and could keep PSA from rising after treatment.

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和文抄録

再燃前立腺癌患者に対するビスホスホネート・低容量デキサメサゾン治療

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われわれは，骨転移による骨痛有するホルモン不応性前立腺癌（HRPC）5例においてビスホスホネート（BP）治療を行い，血清 PSA 値，骨痛と生活の質（QOL）を評価した．インカドロン2ナトリウム（10 mg）を2週ごと，合計6回施行した．治療効果判定を腫瘍マーカー，副作用，QOL，骨痛・疼痛スケールと血液検査で行った．BP 治療は，5例すべて問題なく終了した．治療効果における血清 PSA 値は，1例 PR，2例 NC と2例 PD であった．BP 治療期間中血清Ⅰ型プロコラーゲン値は患者で減少した．しかしながら，血清Ⅰ型コラーゲン値の大きな変化はみられなかった．1人の患者において疼痛の増加が見られたが，他の症例では疼痛の悪化を認めなかった．Short-Form 36（SF-36）による QOL 評価では，全体的健康感以外 BP 治療の間のスコアは不変であった．これらの結果から BP 治療が安全に施行でき，骨痛を伴った HRPC 患者に効果的である可能性が認められ，HRPC に対する治療の1つの選択肢になることが示唆された．

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