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Evaluation of the Effect of Oral Clodronate on Skeletal Metastases with Type 1 Collagen Metabolites. A Controlled Trial of the Finnish Prostate Cancer Group

T. Kylmälä, T. Tammela, L. Risteli, J. Risteli, T. Taube and I. Elomaa

Clodronate relieves bone pain in patients with skeletal metastases. Since the pain relieving mechanism of clodronate may be associated with the antiosteoclastic activity, we have investigated whether the drug has simultaneous actions on bone resorption and pain. Although osteosclerotic metastases are characteristic of prostate carcinoma, bone resorption is also accelerated. The resorbing process can be investigated using a specific immunoassay for ICTP (cross-linked carboxyterminal telopeptide region of type I collagen) which allows the measurement of the degradation of type I collagen in serum samples. We have also determined serum concentration of PICP (carboxyterminal propeptide of type I procollagen) which reflects the synthesis of type I collagen (osteoid). Patients who have relapsed after first-line hormonal therapy, were randomised to receive estramustine phosphate (E) with or without clodronate (C) (E+C, $n = 50$; E, $n = 49$). The dose of E was 560 mg and that of C 3.2 g for the first month, thereafter 1.6 g. We saw elevated ICTP and PICP levels in the majority of the patients. A transient decrease in ICTP values occurred simultaneously with pain relief. The changes were more accentuated in the E+C than in the E group but the difference was not significant. In each group serum phosphate concentration decreased markedly ($P = 0.001$) whereas the activity of alkaline phosphatase remained increased, both indicating a development of oesteomalacia during E therapy. The short-term antiosteoclastic effect of C may be explained by the dose reduction, hyperosteoidosis and osteomalacia which inhibit the binding of C on the crystal surfaces and by the late phase of disease.
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INTRODUCTION

BONE IS the only site of metastasis in 65% of patients with prostate cancer and 80% of patients who die from the disease have bone metastases [1]. Although most of the patients respond to the first-line hormonal therapy, the median survival is between 2 and 3 years and only 30% of patients are alive at 5 years [1]. The response rate to any therapy after first relapse is much less impressive and the median survival is only 4–15 months [1–4]. We have often used estramustine phosphate (E) as a second-line treatment [4].

The main problem of relapsing disease is bone pain. Recently, intravenously administered bisphosphonates have been shown

Table 1. Patients' characteristics, previous treatments, side-effects in the estramustine + clodronate (E+C) and the estramustine (E) groups

	E+C	E
No. of patients	50	49
Mean age (year)	72	71
Range	54–90	47–89
Mean time from initial diagnosis	37	38
Range (month)	3–148	4–170
Histological grade		
G I	7	6
G II	30	36
G III	10	5
Previous treatments		
Orchiectomy	20	22
Oestrogens	18	17
LHRH-agonists	12	10
Discontinuation of the trial because of:		
Nausea and diarrhoea	6	7
Progression	10	14
Death	15	10

to relieve bone pain in patients with skeletal metastases due to prostate cancer [5–9]. We have confirmed pain palliation with oral clodronate (C) in a controlled trial [10].

The mechanisms by which C controls bone pain are not well understood, but they are thought to be a result of decreased bone resorption. Resorbing process in bone tissue can in principle be studied by following the metabolism of type I collagen which is synthetised by osteoblasts and accounts for about 90% of the organic matrix of bone. We have used specific immunoassays for PICP (carboxyterminal propeptide of type I procollagen) and ICTP (cross-linked carboxyterminal telopeptide region of type I collagen) which allow simultaneous assessment of the synthesis and degradation of type I collagen in serum samples, respectively. Thus, PICP should describe bone formation and ICTP bone resorption. We wanted to know whether C reduces bone resorption at the same time as it relieves bone pain, whether it has actions on the findings in bone scintigraphy and whether it influences survival.

PATIENTS AND METHODS

A total of 99 patients with bone metastases from prostate cancer that had failed at least one hormonal therapy were investigated. Entry criteria were intermittent or constant bone pain with daily use of analgesics, no radiation therapy in 2 months preceding or any time during the trial and an estimated life expectancy of at least 3 months. All patients were randomised to receive E (Estracyt 280 mg twice daily) with or without C. The groups were very similar as regarding histological grade, tumour stage and previous therapy (Table 1). C (Bonefos, Leiras) was given orally. The dose was 3.2 g for the first month, 1.6 g thereafter for a further 5 months.

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The effect of treatments was assessed on the presence or absence of bone pain at any skeletal site and on the use of analgesic drugs. Bone scans were evaluated at entry to the study and subsequently updated after 6 months. A group was appointed to evaluate changes in the bone scan. For this analysis the initial scans of 99 patients and sequential scans of 54 patients (26 patients in the E+C group and 28 patients in the E group) have been reviewed by the members of the group independently of each other, of the responsible clinician and of the scan report. To attempt a similar semiquantitative analysis a form according to Soloway *et al.* [11] and Smith *et al.* [12] was designed to allow the recording of the number of hot spots in the different areas of the skeleton. When a difference between the evaluations of two members was noted, the third of the members was asked. A consensus was made 15 times (10%). Only twice (4%) was the evaluation of response different between two observers and regarded the evaluation of stable from progressive disease. The NPCP criteria for response evaluation and WHO recommendation for side-effects were used [13, 14].

Serum calcium, phosphate, alkaline phosphatase (AP), prostatic acid phosphatase (PAP) and prostatic specific antigen (PSA), creatinine and transaminase levels were determined before the trial and after 1, 3 and 6 months. Similarly serum was collected for measurements of type I collagen metabolites (PICP and ICTP).

Radioimmunoassays for collagen metabolites

The radioimmunoassay for analysing the concentration of PICP has been established by isolating type I procollagen from the medium of primary cultures of human skin fibroblasts and by digesting it with highly purified bacterial collagenase to liberate PICP [15]. The concentration of PICP was measured in duplicate 100 μl serum samples with an equilibrium radioimmunoassay, obtained from Orion Diagnostica (SF-90460 Oulunsalo, Finland). The sensitivity of the test is 1.2 μg/l. The intra-assay coefficient of variation was around 3%. The corresponding interassay variation was about 5%. The reference interval (mean + 2 S.D.) for women (18–61 years of age) is 50–170 μg/l, with no apparent correlation with age, and for men (18–61 years) 50–200 μg/l, with an inverse correlation with age [15]. The serum PICP antigen is stable upon repeated freezing and thawing and for several years of storage at −20°C [15].

ICTP was liberated from decalcified human femoral bone, removed during hip surgery, by digesting with bacterial collagenase or trypsin. The cross-linked peptide was purified by two successive reverse-phase separations on high performance liquid chromatography (HPLC) and its identity verified by N-terminal amino acid sequencing. Polyclonal antibodies against the telopeptide region were produced in rabbits and the peptide labelled with the chloramine T-method. In a radioimmunoassay serum samples give inhibition curves parallel with the standard antigen, indicating that during normal bone turnover a similar fragment is set free and remains immunochemically intact. In gel filtration analysis of serum only one peak of low molecular weight is found. An equilibrium type of immunoassay was developed using 100 μl samples and taking 4 h to perform [16]. The reference interval of ICTP in normal human serum (n = 44) is between 1.5 and 4.0 μl/l. A commercial version of the assay is available from Orion Diagnostica. The intra- and interassay coefficients of variations of the method are about 5–7%, respectively. The serum ICTP antigen is stable during storage at −20°C for several years (unpublished data).

Statistical analysis

The significance of differences of the means between and within the groups was established by the *t*-test. The McNemar test was used for analysing changes of pain relief within patients of each group and χ^2 test for comparing differences between treatment groups. Product-limit survival analysis was performed for comparing survival between the groups. Analyses were performed using BMDP-PC90 (Statistical Software Inc., Los Angeles, California).

RESULTS

Bone pain

Pain relief appearing within 1 month and reduction of the use of analgesics were more accentuated in the E+C group than in the E group (P = not significant within and between the groups) (Fig. 1). The dose of 3.2 g of clodronate seemed be more effective than 1.6 g.

Biochemical determinations

Serum calcium and phosphate concentrations decreased significantly in both groups during the treatment ($P = 0.001$) (Table 2). The mean activity of serum AP remained high during the study and showed no significant changes in either of the groups (Table 3). The levels of PAP and PSA behaved similarly (Table 3).

At study entry high serum ICTP values were seen in 76% of the E+C group and 70% of the E group. Similarly elevated serum PICP values were found in 56% of the E+C arm and 61% of the E arm, and an increased serum AP activity in 68% of the E+C group and 73% of the E group. The ICTP values declined at 1 month in both groups and increased after 3 months, remaining a little lower in the patients with C (Fig. 2). A decrease in PICP levels was observed up to 3 months in both groups, but in the E+C group the values still declined after 3 months whereas in the E group the values increased (Fig. 2). There were no significant differences between the groups.

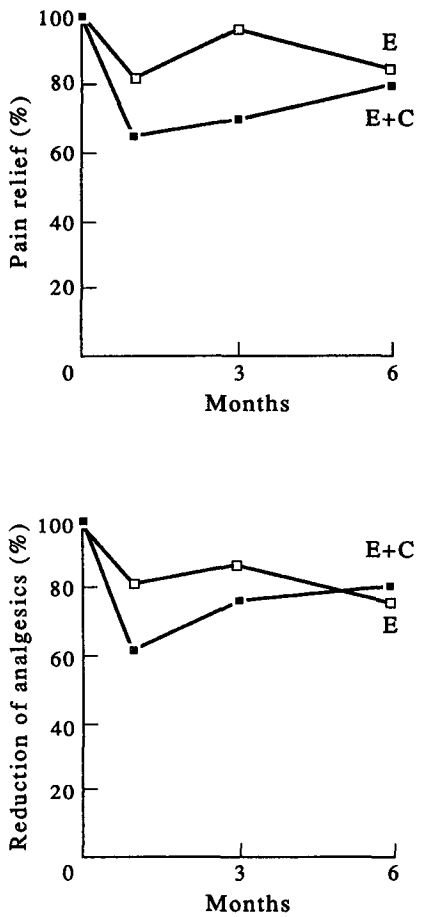


Fig. 1. Percentage of patients free of bone pain (top) and without analgesics (bottom) during the study in E and E+C groups.

Table 2. Serum calcium (S-Ca) *and phosphate* (*S*-Pi) *concentrations during the trial*

Determination (reference range)	E+C No.	E+C Mean	E+C S.D.	E No.	E Mean	E S.D.	*P*
S-Ca (2.20–2.65 mmol/l)							
0 months	49	2.30	0.11	49	2.28	0.17	ns
1 months	43	2.20	0.15	43	2.21	0.14	ns
3 months	36	2.17	0.16	36	2.19	0.13	ns
6 months	23	2.20	0.15	20	2.17	0.17	ns
S-Pi (0.84–1.40 mmol/l)							
0 months	49	1.01	0.20	49	1.02	0.23	ns
1 months	43	0.90	0.26	43	0.79	0.15	ns
3 months	36	0.82	0.28	36	0.75	0.14	ns
6 months	23	0.77	0.17	20	0.83	0.14	ns

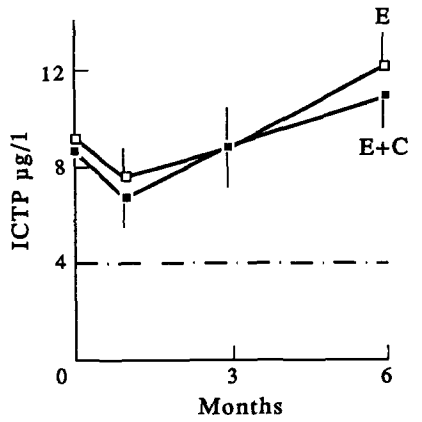
$P < 0.001$ when the means between the entry and 6 months are compared within the groups. ns, Not significant.

Bone scan

The sites and number of bone metastases at entry of the study and after 6 months are given in Table 4. The response rates are illustrated in Fig. 3. No significant changes regarding the response rates between the groups at entry or at 6 months of therapy were observed.

Table 3. Levels of various markers during the study

Marker (reference range)	E+C Mean	E+C S.D.	E Mean	E S.D.	*P*
AP (60–275 U/l)					
0 months	723	731	1016	1049	ns
1 months	796	656	968	878	ns
3 months	779	754	878	867	ns
6 months	768	621	1116	1134	ns
PAP (< 3 μg/l)					
0 months	38	52	50	77	ns
1 months	30	34	44	74	ns
3 months	43	62	33	59	ns
6 months	31	38	43	54	ns
PSA (< 4 μg/l)					
0 months	335	563	240	297	ns
1 months	192	225	201	263	ns
3 months	213	280	254	704	ns
6 months	448	708	214	229	ns
PICP (50–200 μg/l)					
0 months	328	344	250	167	ns
ICTP (1.5–4.0 μg/l)					
0 months	8.8	6.7	9.1	6.1	ns



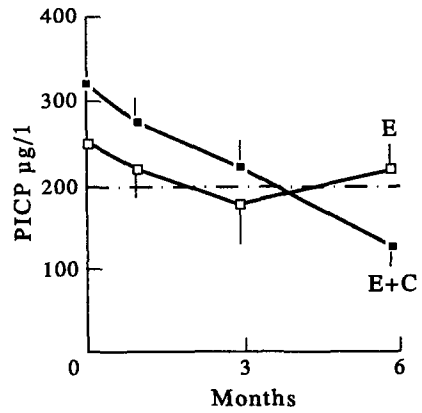


Fig. 2. Changes in the levels of ICTP (top) and PICP (bottom) during the study in E and E+C groups. The values are means + S.E. Broken line represents the upper limit of the reference range.

Survival

There were no significant differences in median survival (10 months in E+C, 12 months in E) or survival rate (70% in E+C and 75% in E at 6 months) between the groups ($P = 0.11$ Mantel–Cox, $P = 0.15$ Breslau).

Table 4. Sites of bone metastases at entry on the study and at 6 months after therapy. E+C = the group receiving estramustine and clodronate and E the group receiving only estramustine

	E+C		E		
Site	Mean	(Range)	Mean	(Range)	*P*
Skull	1	0–6	1	0–8	
Cervical vertbrae	1	0–6	1	0–5	
Thoracic vertebrae	5	0–20	4	0–17	
Lumbar vertebrae	3	0–14	3	0–10	
Pelvis	6	0–12	6	0–11	
Femur	1	0–6	1	0–6	
Humerus	2	0–9	2	0–17	
Scapulae	1	0–6	1	0–6	
Ribs	9	0–24	8	0–30	
Total					
At entry	29	2–68	27	2–71	ns
At 6 months	40	4–90	43	3–103	ns

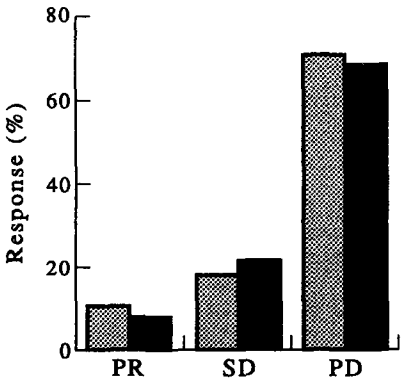


Fig. 3. Response rates evaluated in bone scintigraphy in the E (grey) and E+C (black) groups. PR = partial response, NC = no change, PD = progressive disease.

DISCUSSION

C has relieved bone pain in patients with metastatic breast and prostate cancer, multiple myeloma and Paget's disease of bone [5–10, 17–19]. Mechanisms of pain relief have remained unclear but they are probably related to antiosteoclastic activity of the drug which reduces acute inflammatory reaction and bone resorption.

Although osteosclerotic metastases are characteristic of prostate cancer, bone resorption is also accelerated, as evidenced by an increase in the urinary hydroxyproline excretion, by the presence of lytic bone lesions in X-rays [20, 21] and confirmed by histomorphometric examinations of tumour-bearing and tumour-free skeletal biopsy specimens [22–24]. An increased influx of calcium into bone would decrease serum calcium and stimulate the secretion of parathyroid hormone, resulting as an acceleration of bone resorption [25]. Lastly, bone loss may be increased by androgen deprivation. In some cases the lytic lesions may lead to pathological fractures and hypercalcaemia, which cause morbidity and mortality. Thus, the use of inhibitors of bone resorption like C are well founded.

Most of our patients had increased ICTP levels which indicates acceleration of bone resorption. C decreased the concentration of serum ICTP, but so did E. The reduction in bone resorption and bone pain occurred simultaneously and transiently. Although the change was more accentuated in E+C than in the E group, there was no significant difference between the groups. This raises the question, is it the ICTP assay, or the C that is not working?

In a recent study in multiple myeloma ICTP has been correlated positively with urinary hydroxyproline excretion, lytic radiographic lesions and progressive osteolysis [26]. Methods of calcium kinetics and dynamic histomorphometry have shown a significant correlation between serum ICTP concentration and bone resorption in a group of patients with high bone turnover [27]. Thus, ICTP has functioned well as a marker for bone resorption.

The fact that ICTP level decreased during C therapy only transiently, is surprising and may be a result of the dose reduction. Another cause is probably the accumulation of collagen (osteoid) in skeletal metastases, which might reduce C binding on crystal surfaces and thus cause the inefficacy of the drug [28]. An additional cause of the insufficiency of C may be the E-induced osteomalacia which was indicated by the significantly falling serum phosphate concentration in both groups. Simultaneously the activity of serum AP was maintained

at a high level, supporting the continuous hyperfunction of osteoblasts. Indeed, we have considered histomorphometrically a development of osteomalacia in patients receiving E therapy (to be published). Thus, the combination of C with E seems to be unwise.

Since the ICTP level decreased in both treatment groups, E must have inhibiting actions on osteoclasts. Because the effect of C on ICTP level was not much better than E only, C was not potent enough to inhibit bone resorption. Besides dose reduction and osteomalacia, a further cause was probably the late phase of prostate cancer where the tumour burden is too large for effective therapy. Therefore, it may be rational to use C earlier, e.g. at the time bone metastases appeared.

ICTP is cleared by the kidneys [26]. Thus, the levels can also increase, if the patients have severe renal failure, which our patients had not.

Also the PICP levels were elevated at study entry in the majority of the patients which is a result of overactivity of osteoblasts. The levels, however, decreased towards the terminal phase. One explanation for this behaviour is probably insufficient collagen synthesis due to enhanced catabolism and tumour cachexia in the late phase of disease. The other cause may be cancer therapy which through the reduction of tumour burden leads to diminished activity of the osteoblasts. However, the analgetic and antiosteoclastic effects of E were transient. Response rate was poor which was seen as continuously elevated serum PAP and PSA concentrations and increased number of new lesions in bone scintigraphy, where C had no interfering actions on tracer uptake and distribution in bone scan.

We conclude that although serum ICTP level was elevated in the majority of the patients, C was unable to decrease the ICTP level significantly more than E only. The explanations for the poor efficacy of C were probably (1) the dose reduction and (2) the insufficient binding of C on bone surfaces because of hyperosteoidosis and osteomalacia which developed during E therapy as well as (3) the late phase of prostate cancer.

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