Chronic Treatment of Paget's Disease of Bone
with Synthetic Human Calcitonin

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Twelve patients with Paget's disease of bone were treated with synthetic human calcitonin for seven to 26 months (mean 15.3 months). This group included six patients who had previous therapy. Eleven of the 12 patients experienced relief of the symptoms associated with Paget's disease.

The initial therapy of synthetic human calcitonin 0.5-1.0 mg subcutaneously was administered daily until the alkaline phosphatase had declined to a plateau response; the dose was then decreased to thrice weekly.

The major biochemical findings were a 47 percent fall in serum alkaline phosphatase and a comparable decline in 24-hour urinary hydroxyproline. Two subjects discontinued therapy because of side effects; persistent nausea and vomiting in one and a cutaneous allergic reaction in the other. Other side effects were minor.

Preliminary results suggest that some patients will maintain the same biochemical response on the reduced dose but that this is not predictable by pre-treatment data.

We conclude that synthetic human calcitonin is a safe and effective treatment for Paget's disease of bone. Preliminary results suggest that the dose and frequency of administration of this agent must be individualized.

Calcitonin (CT) has been shown to be both safe and effective in the treatment of patients with Paget's disease of bone (PD) [1–3]. Shortly after porcine calcitonin was introduced, salmon calcitonin (SCT) was found to be the most potent of the various forms of calcitonin available [4]. However, it soon became apparent that a substantial number of patients developed resistance to treatment with porcine or salmon calcitonin [5,6]. Although there has been some controversy as to the pathogenesis of this resistance [5–7], it is now generally accepted that the major factor responsible is the development of species-specific neutralizing antibodies [7,8].

Synthetic human calcitonin (HCT) was reported to be effective in the treatment of PD about ten years ago and resistance has not been seen [2,9]. However, because of difficulty in synthesizing large quantities of HCT, it was not available for large-scale trials in many centers until relatively recently. Therefore, there are few reports in the

literature documenting its efficacy, particularly since 1977 when a more purified preparation became available [10].

Here we report the results of long-term treatment (7–26 months) with human calcitonin in 12 patients with PD. Of particular interest are the results in eight subjects who had undergone previous treatment, including seven who had received SCT. In addition, preliminary results of studies evaluating the lowest effective dose are presented.

MATERIALS AND METHODS

Patient Population

Twelve patients with previously diagnosed PD were included in the study. Initially, because of the limited supply of HCT, only patients who had allergy to or side effects from SCT were admitted. However, starting with patient 5, the admission criteria were liberalized to include anyone with PD who volunteered to be included in the protocol.

Table 1 summarizes the frequency of signs and symptoms related to PD in the twelve subjects. Table 2 contains pertinent clinical data and information about previous therapies for each of the twelve patients.

Pre- and Post-Treatment Evaluation

All patients were admitted to the Clinical Research Center, Yale–New Haven Hospital, for baseline evaluation before initiation of HCT therapy. The eight subjects who had completed more than nine months of treatment were readmitted for post-treatment evaluation.

The following baseline analyses were performed while fasting: complete blood count with differential, serum electrolytes, BUN, magnesium, calcium, phosphorus, creatinine, uric acid, alkaline phosphatase, acid phosphatase, total protein, fasting blood glucose, total and direct bilirubin, SGOT, 5' nucleotidase, thyroid indices, PTH, and protein electrophoresis. The diet contained 400 mg calcium, 800 mg phosphorus, 1.0 gm/kg protein, and was low in gelatin.

At least two 24-hour urine collections were assayed for calcium, phosphorus, creatinine, and hydroxyproline. Selected skeletal films and a bone scan were performed during each inpatient evaluation. Yearly audiograms were performed using standard technique.

TABLE 1
Frequency of Signs and Symptoms Related to Paget's Disease in the 12 Subjects

	No. Affected
Pain (including headache)	11
Hearing loss	9
Decreased mobility	6
Increased skin temperature over Pagetic bone	6
Skull enlargement	5
Bowing of long bone	3
Non-traumatic fractures*	3
Nephrolithiasis	3
Gout	2
Hydrocephalus	1

*One subject had three fractures and another had two.

TABLE 2
Clinical Features, Biochemical Findings and Previous Treatment of Subjects

Pt	Age	Sex	Yr of Paget's	Prior Treatment			Pre-treatment		Symptoms and Signs^Δ
				Drug*	Duration	Reason to Stop†	AP‡	Hypro§	
1	69	M	17	SCT	9 mo	Res	702	188	ha; ↓AD; ks; ↑hs; Basilar invagination; ↑T skull
2	55	M	6	SCT	6 mo	Res	2,500	538	↓AD; pain L fem & pa; ↑head size; fx L cl, fem & pa; ↑T L pa
3	64	F	27	SCT	8 mo	N&V	320	212	pain R hip, knee, tib; bp; ↓mob; ↑T R & L Fem, L rad
4	74	F	8	SCT Mith	1 day 3 wk	Rash N&V	102	87	L hip pain; ↓mob. ↓AU
5	77	M	7	None			218	99	↓AU; ks; ↓mob; fx R fem, L tib
6	90	F	17	Analgesics			158	50	Pain R sho, neck, L groin; fx R leg x2; ↑T R fem; ↓mob
7	60	M	5	Etid	6 mo		28	18	R fem pain; ↑T R fem; ↑hs; ↓AU; gout
8	60	F	30	X-ray to pelvis NaF SCT	18 mo	Res	537	220	ha; bp; pain R, L fem; fx LV; ↓mob; ↓AU
9	69	M	0.5	None			165	89	R hip pain; ↓mob; ↓AU
10	60	F	2	SCT	14 mo	Res	1,080	339	ha; ↓AU; bp
11	59	M	5	None			720	192	ha; ↓AU; ks
12	72	M	2	SCT Etid	2 mo 2 wk	N&V Rash	221	58	bp; gout

*SCT = salmon calcitonin, mith = mithramycin, NaFl = sodium fluoride, Etid = etidronate
†Res = resistance; N&V = nausea and vomiting
‡serum alkaline phosphatase (normal < 70 IU/dl)
§24 hour urine hydroxyproline (normal < 45 mg),
Δha = headaches; ↓ = decreased; AD = hearing right ear; AS = hearing left ear;
AU = hearing both ears; ↓ = decreased; ks = kidney stones; ↑ = increased; hs = head size,
fx = fracture; cl = clavicle; fem = femur; pa = patella; tib = tibia; LV = lumbar vertebra;
rad =radius; sho = shoulder; R = right, L = Left, bp = back pain; mob = mobility;
T = temperature.

On the last day of the hospitalization, calcitonin treatment was initiated.

Follow-Up Outpatient Visits

Every 6–8 weeks, subjects were seen and evaluated for subjective (pain relief, side effects of medication, etc.) and objective improvement. The latter included blood samples for calcium, phosphorus, alkaline phosphatase, creatinine, and parathyroid hormone (PTH). Twenty-four-hour urine collections for calcium, phosphorus, creatinine, and hydroxyproline were done every 3–4 months.

Analyses

All laboratory analyses were done in the clinical chemistry laboratory of Yale–New Haven Hospital except for immunoreactive PTH; this was sent to Nichols Institute, San Pedro, California.

Serum and urine calcium were measured by atomic absorption spectrophotometry. Alkaline phosphatase was determined by the revised method of McComb and Bowers [11]. Phosphorus was estimated by a continuous flow method. Hydroxyproline was measured by the method of Parekh and Jung [12].

Calcitonin Administration

The treatment period covered by this report ranged from 7 to 26 months (mean 15.3 months). The dose of HCT administered ranged from 0.5 mg three times weekly to 1.0 mg daily. Ten subjects were started on 0.5 mg subcutaneously daily and two (patients 5 and 6) 1.0 mg daily because of severe complications of Paget's disease (two recent fractures and intense pain, respectively). In eight patients the dose of HCT was changed during the course of the study. Decreases from 0.5 mg daily to 0.5 or 1.0 mg three times per week were made after the patient had a plateau in the clinical and/or biochemical response. Patients 8 and 11 had their doses increased from 0.5 to 1.0 mg daily because of persistent symptoms, and patient 2 was increased from 0.5 to 1.0 mg daily because of partial biochemical rebound (without worsening of symptoms); he was later decreased to 1.0 mg thrice weekly.

RESULTS

Clinical Observations

Ten of the twelve patients tolerated the medication well. Side effects were generally minor and were principally limited to the first one to two hours post injection. These included mild nausea (eight patients), local warmth and/or erythema at the site of injection (two patients), flushing (two patients), hyperdefecation (one patient), "chilly sensation" (one patient), and eructation (one patient). In many patients these symptoms gradually decreased or disappeared entirely during the first few weeks of therapy.

Three patients discontinued HCT therapy: subject 3 (after 9.5 months) because of significant side effects (persistent nausea and vomiting) and only modest symptomatic improvement, patient 6 (after 9 months) because of an apparent allergic (urticarial) reaction, and subject 7 because of relocation.

Eleven patients experienced symptomatic improvement, in most cases by 1–3 months after starting HCT. This consisted of the relief of bone pain and headache, a decrease in skin temperature, and/or an increase in mobility. The recent fractures in patient 5 healed normally. A few patients continued to have some pain, thought to be due to concomitant arthritis and/or far-advanced deforming PD of the lower

extremities. No patient experienced a worsening of symptoms, and no patient sustained a fracture while on therapy. None of the nine patients who had hearing loss experienced any subjective or objective improvement.

Biochemical Studies

As noted in Table 2, AP was initially elevated (greater than 70 IU/dl) in 11 of the 12 patients, ranging from 102 to 2,500 with a mean of 611 ± 698 (SD). Patient 7, who also had primary hyperparathyroidism and had been treated previously with sodium etidronate, began calcitonin therapy with a normal AP of 28 IU/dl. In 10 of the 11 patients with pre-treatment elevations in AP, the AP dropped to an average of 47 percent of pre-treatment values (range of 24–72 percent) (Fig. 1). In these patients, the AP gradually decreased over the first 30 weeks of treatment and then leveled off.

The individual AP data for the 10 patients are shown in Fig. 2. Three subjects reached AP values within the normal range. One patient (2) experienced a biochemical rebound. Initially he had a significant response, decreasing his AP from 2,500 to 1,630 (65.2 percent) in six months. Over the next few months it gradually rose, and, despite an increase in his dose from 0.5 mg to 1.0 mg daily, it continued to rise, peaking at 2,200. This was not accompanied by an increase in hydroxyproline excretion, and his previously mild symptoms remained unchanged. Elevation of the AP during treatment was also seen in patient 1 and patients 4 and 9, whose dose of HCT was decreased to 1.0 mg three times a week and 0.5 mg three times a week, respectively. The HCT dosage in patients 2 and 5 was decreased to 1.0 mg three times a week, and they remained unchanged both clinically and biochemically.

The degree and the rate of decline of the AP values were not related to the initial dose of HCT. However, there was a tendency for subjects with the highest AP to have the smallest percent age of decrease with treatment.

Urinary hydroxyproline (Table 1) was initially elevated in all except patient 7. Data on hydroxyproline excretion over the course of therapy was obtained for seven subjects. The mean (±SD) 24-hour excretion for these patients at the onset of therapy was 222.7 ± 166 mg (range of 87–537.5 mg) with normal less than 45 mg. Figure 3 shows the urinary hydroxyproline vs. duration of therapy (in weeks) for seven patients, irrespective of dose. As with the AP response, the maximum decrease
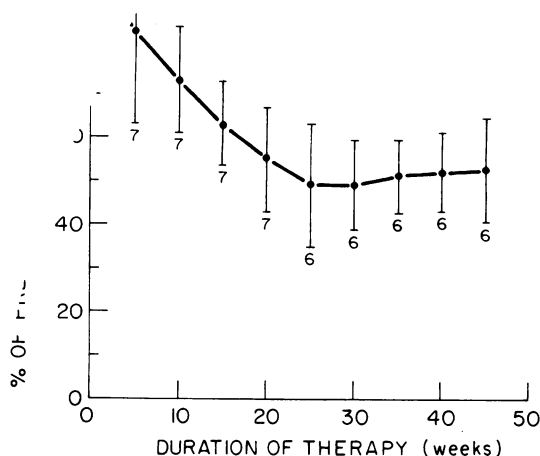

FIG. 1. Mean (± S.D.) alkaline phosphatase expressed as the percentage of the prehuman calcitonin treatment value for the 10 subjects who had pre-treatment values uninfluenced by previous therapy (see text). Patients 3 and 7 were excluded. The number under the bars is the number of subjects for each treatment period. There was no change from week 55–100 (not shown).
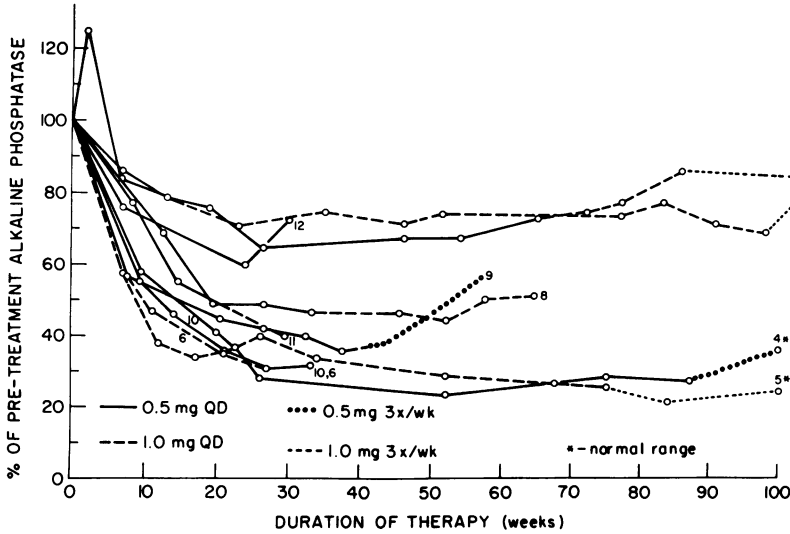
FIG. 2. Individual pre- and post-human calcitonin alkaline phosphatase values
for subjects in Fig. 1. The dose of calcitonin is depicted for each subject by the sym-
bols noted above. The patient numbers from Table 2 are next to the respective curve.
Subjects whose post-treatment alkaline phosphase fell to the normal range are iden-
tified by an asterisk (*).

occurred after approximately 25–30 weeks of HCT therapy, with hydroxyproline ex-
cretion leveling off at an average of 47 percent of the original mean value (range of
26–60 percent). Figure 4 shows the hydroxyproline response for the individual pa-
tients. The asterisks identify three patients (4,5, and 9) whose hydroxyproline excre-
tion fell into, or very near (9), the normal range. Two patients had rebound eleva-
tions: patient 1, from a low of 54 percent of baseline value at 28 weeks to 92 percent
at 65 weeks, and patient 8, from a low of 35 percent at six weeks to 80 percent after
one year. This was not accompanied by a change in symptoms or an increase in AP.

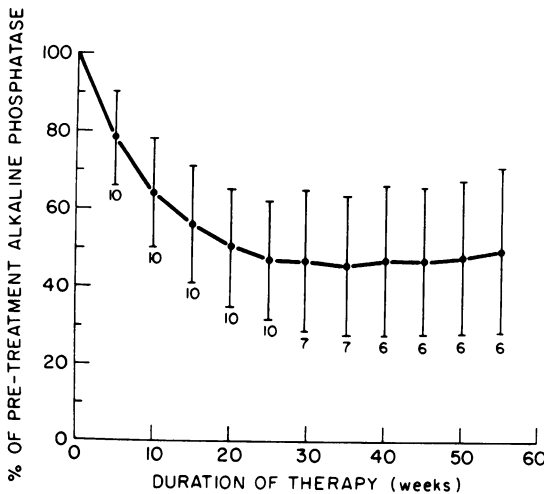Serum levels of calcium and PO_4 were within normal limits for 11 of the subjects

FIG. 3. Mean (± S.D.) 24-hour urine
hydroxyproline values during treatment ex-
pressed as the percent of the pre-human
calcitonin treatment value for seven sub-
jects who had elevated values. The number
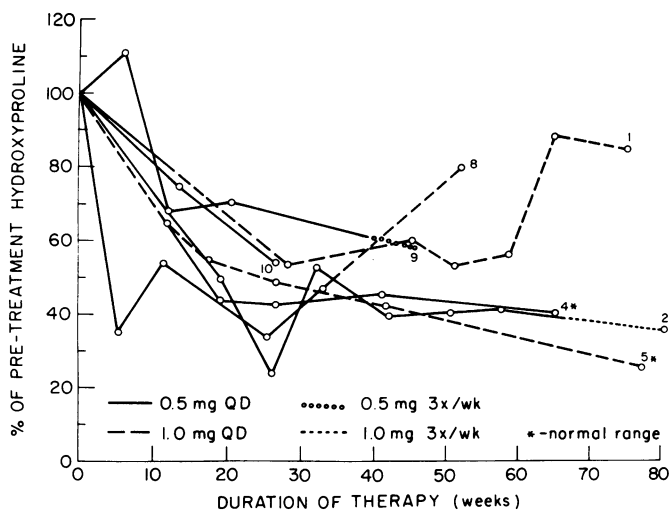under the bars is the number of subjects for
each treatment period.

FIG. 4. Individual 24-hour urine hydroxyproline value for the subjects in Fig. 3. Same format as Fig. 2.

throughout the study. Patient 7, with primary hyperparathyroidism, had a modestly elevated serum calcium and a low serum PO_4, neither of which changed with HCT treatment. The 24-hour urine calcium was normal in all subjects before and after HCT therapy. Other blood studies, including PTH, uric acid, BUN, bilirubin, SGOT, thyroxine, protein electrophoresis, and complete blood count with differential did not change during the treatment period.

There was an excellent correlation between the X-rays and bone scans. In 100 percent of sclerotic/deformed bones on X-ray, the bone scan was positive. There was only one instance in which there was a positive scan without definite corresponding radiologic involvement. Patient 3 had increased uptake in the skull; her skull X-ray showed prominent vascular channels, indicative of uniform demineralization. This pattern is consistent with early PD given the presence of PD in other areas of the skeleton. There were no instances of diseases seen on X-ray but not by bone scan.

Seven subjects had a second set of skeletal films and bone scans taken after approximately one year of therapy. Four (patients 3,4,7,8) had no change, and three (subjects 1,2, and 5) had decreased uptake on bone scan. Only one patient (2) had a change noted on X-ray: a decrease in the size of a lytic area of his left proximal femur without a corresponding change in his bone scan.

Bone Biopsies

All patients in the study underwent iliac crest bone biopsies prior to treatment with HCT. Six subjects had a second biopsy performed after one year of HCT. All biopsies were characteristic of PD, and post-treatment biopsies revealed a decrease in active resorption surface in pagetic areas.

DISCUSSION

Paget's disease is a chronic condition characterized by an extremely high turnover rate of bone [14]. It has been shown that pharmacologic agents which slow bone remodeling to or toward normal are accompanied by evidence of improvement (see below) [1-3,8]. Of the various agents which have been shown to be effective, calcitonin has been found to be the safest [8]. Since 1967 salmon, porcine, and human calcitonin have been used in the management of PD [1-3]. Numerous studies

have demonstrated subjective improvement, including pain relief and increased mo-
bility in pagetic patients [8]. This has been accompanied by objective changes such as
lowering of the serum AP and the urinary hydroxyproline values [1-3,8], radiologic
regression of early PD [2], and histomorphometric evidence of normal bone forma-
tion in pagetic areas [9]. Generally, the above biochemical parameters decrease to 50
percent of pre-treatment levels after six months of CT treatment, then plateau for
the duration of treatment [8]. Symptomatic relief is maintained without any further
decrease in the biochemical values, which, while significantly decreased, may still be
well above the normal range. The failure of the AP to fall to normal cannot
necessarily be interpreted as an incomplete response because it has been shown that
therapy is associated with the formation of normal lamellar bone in previously
pagetic areas of bone even in the presence of elevated AP. Conversely, a fall of AP
into the normal range, as is frequently seen in etidronate-treated patients, may be ac-
companied by increased bone pain, generalized skeletal demineralization, and an in-
crease in the number of fractures [15]. Thus, the biochemical response does not
necessarily reflect efficacy. At best, it will confirm subjective impressions, but it
may be completely misleading as with some etidronate-treated patients [15].

"Resistance" to the action of SCT develops in up to 40 percent of treated patients
[5-8]. This is characterized by a rebound in alkaline phosphatase and hydroxyproline
levels and a re-emergence of symptoms [5-8]. At the present time, most authorities
agree that this resistance is usually due to the presence of neutralizing antibodies to
the non-human calcitonins [6-8]. HCT has been shown to be active in these patients
in the presence of neutralizing antibodies to SCT [7].

The largest study of HCT came from the Hammersmith Hospital where patients
with PD have undergone long-term therapy with HCT since 1969 [2,9,16]. As with
SCT, significant symptomatic improvement was achieved in the majority of pa-
tients, and there was a plateau in AP and hydroxyproline to approximately 50 per-
cent of pre-treatment values after six months of therapy [16]. The present study con-
firms these findings. None of the patients in the Hammersmith trial developed
resistance to the medication, no antibodies to HCT were detected, and, while a few
patients could be called "non-responders," clinical or biochemical relapse was un-
common [16]. It was concluded that HCT was non-immunogenic [13,16]. In our
study, patient 6 developed an urticarial reaction without clinical or biochemical
relapse (Fig. 2). Preliminary studies suggest that this patient was allergic to the
HCT; detailed studies of her immunologic response to HCT are in progress and will
be reported in detail separately. Only one patient has been reported to have
developed antibodies to human calcitonin [17] and she did not have an allergic reac-
tion or relapse of her PD [17].

Three of our patients showed some biochemical relapse while on a level or increas-
ing dose of HCT. The AP (but not the hydroxyproline) in patient 2 began to increase
gradually after almost 55 weeks of therapy and continued to rise despite an increase
in HCT dose (Figs. 2 and 4). Patients 1 and 8 had rebounds in hydroxyproline
without a change in AP (Figs. 2 and 4). In our hands, hydroxyproline is a less ac-
curate indication of disease activity than serum AP levels, because urinary hydroxy-
proline values may vary with diet [18] and some of these measurements were made
on 24-hour outpatient urine collections without strict dietary control of gelatin in-
take. Only patient 1 had concomitant return of pain, but this was not to pre-
treatment levels. None of these three patients had a significant rise in antibody titer
to HCT. Alternative explanations which have been offered for the phenomenon of
biochemical rebound without the development of neutralizing antibodies are

hypophosphatemia [19], secondary hyperparathyroidism [20], and the "escape" phenomenon [21]. PTH levels were within normal limits for all of our patients throughout the treatment period, with the exception of patient 7, who also had primary hyperparathyroidism. Although calcitonin has been shown to be phosphaturic, none of the patients in our study developed hypophosphatemia, similar to the experience of most other investigators [8]. The so-called "escape" phenomenon has been demonstrated *in vitro* [21] but not *in vivo* so that we cannot assess the role of "escape" in the biochemical rebound in our subjects.

Because of the long biologic half-life of SCT, many patients will experience full benefit from as little as 1–3 doses weekly [22,23]. Since the half-life of HCT is shorter than SCT, one would expect that more frequent administration would be necessary. This was confirmed in the Hammersmith study [2,16]. However, in 1977, after most previously published studies had been completed, the manufacturer announced that HCT was being highly purified [10]. They recommended initial treatment with 0.5 mg daily, followed by maintenance with 0.5 mg two to three times weekly [10]. Therefore, we did some preliminary trials with thrice weekly therapy. Five subjects (patients 1,2,4,5, and 9) had sufficient follow-up data for assessment. Three subjects (1,4, and 9) had a modest rise in their alkaline phosphatase, and the other two had no change. Hydroxyproline values were available for two subjects (2 and 9), and there was no change. In this small group, it was not possible to predict from the severity, extent, or activity of the PD which subjects would be controlled on the three times weekly schedule. Furthermore, two of the three subjects who had a rise in AP did not have return of their previous symptoms. Patient 1, who did have partial return of his symptoms associated with the decreased dose of HCT, did not improve after reinstitution of daily therapy. These results, although preliminary, suggest that the frequency of therapy must be individualized.

Radiologic regression of PD has been seen in patients with early disease after long-term HCT treatment [2]. Once sclerotic changes have occurred, however, the radiologic patterns change little, if at all, with therapy. Doyle et al. [24] demonstrated a dose-related radiologic response to long-term (10–40 months) HCT treatment. Five of 11 patients treated with 0.5 mg twice a day showed improvement, while the other six had no change. Three of 14 patients on 0.5 mg per day showed regression, four showed deterioration, and seven had no change. In 15 patients on doses of less than or equal to 0.5 mg three times per week, five deteriorated, 10 had no change, and none showed improvement. None of the patients who demonstrated radiologic regression in at least one bone showed advance of disease in other bones [24].

In our study, correlation between pre-treatment X-rays and bone scans was excellent. Seven patients had follow-up studies after one year of HCT therapy. Two subjects (3 and 7) had residual biochemical evidence of response to previous treatment (salmon calcitonin and etidronate, respectively) and thus would not be expected to show a post-HCT response on bone scan because bone turnover had already been suppressed by the prior treatment. Another subject, who was previously untreated, had no change in the bone scan. Three patients with sclerotic lesions showed improvement on bone scan without corresponding changes in their radiographic patterns. Only patient 2 had radiologic regression of disease, a decrease in the size of a lytic lesion in his left femur. This was too small an area to be picked up by his bone scan which was "hot" in the entire surrounding femur.

In conclusion, this study confirms earlier investigations demonstrating the effectiveness of HCT in the treatment of PD. The majority of symptomatic patients have

dramatic reductions in pain and increased mobility, with a minimum of side effects. There was no evidence of toxicity except for one subject who developed an apparent cutaneous allergic reaction. Only one patient had bothersome side effects (nausea) from the medication. Treatment was accompanied by a 47 percent reduction in AP and hydroxyproline values; in the few patients with mild disease, these fell into the normal range. We confirm that radiologic regression may occur in lytic areas but that in all probability sclerotic lesions will not show improvement with HCT therapy.

ACKNOWLEDGEMENTS

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