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Cinacalcet Hydrochloride Reduces the Serum Calcium Concentration in Inoperable Parathyroid Carcinoma

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Background: Management of inoperable parathyroid carcinoma presents a challenge because until recently, effective medical therapy was not available. Morbidity and mortality result primarily from severe hypercalcemia. We assessed the ability of the calcimimetic cinacalcet HCl to reduce serum calcium in patients with parathyroid carcinoma as well as its effect on PTH concentrations, bone turnover markers, safety, and health-related quality of life variables.

Methods: Twenty-nine patients with parathyroid carcinoma were enrolled in this open-label, single-arm study consisting of titration and maintenance phases. Cinacalcet doses were titrated (30 mg twice daily to 90 mg four times daily) for 16 wk or until serum calcium was no more than 10.0 mg/dl. The study endpoint was the proportion of patients with at least a 1 mg/dl reduction in serum calcium at the end of the titration phase (responders).

Results: Mean (± SE) serum calcium (14.1 ± 0.4 mg/dl) and PTH (697 ± 94 pg/ml) were markedly elevated at baseline. At the end of the titration period, serum calcium was reduced by at least 1 mg/dl in 62% of patients (mean decline to 12.4 ± 0.5 mg/dl). In the 18 responders, serum calcium fell from 15.0 ± 0.5 to 11.2 ± 0.3 mg/dl ($P <$ 0.001). The greatest reductions in serum calcium were observed in patients with highest baseline calcium levels. PTH levels decreased, but not significantly, to 635 ± 73 pg/ml (−4.6%). Adverse events included nausea, vomiting, headache, and fracture.

Conclusions: Cinacalcet effectively reduces hypercalcemia in approximately two thirds of patients with inoperable parathyroid carcinoma and may represent an important new treatment option for these patients. **(*J Clin Endocrinol Metab* 92: 3803–3808, 2007)**

PARATHYROID CARCINOMA, a rare cause of primary hyperparathyroidism (1, 2), typically results in more profound clinical manifestations than those seen with much more common benign tumors of the parathyroids (3). Although early *en bloc* resection of the primary parathyroid tumor is the only curative treatment, recurrence is common (4). When recurrence occurs by local or distant metastases, surgical removal of malignant tissue provides palliative relief (5), but recurrence occurs generally within 3 yr after parathyroidectomy. The 5-yr survival rate after recurrent parathyroid carcinoma is approximately 50% (3). Medical approaches for refractory and metastatic disease are limited (6) because parathyroid carcinoma is largely unresponsive to chemotherapy or radiotherapy.

After surgical options are exhausted, clinical management generally turns to controlling hypercalcemia. Saline infusion and loop diuretics are often used. Plicamycin is effective, but the response is transient, and repeated courses may be associated with toxicity (3). Potent iv bisphosphonates may control hypercalcemia transiently; however, patients frequently become refractory to them. Because the primary cause of mortality is PTH-driven hypercalcemia, rather than direct tumor invasion or spread, a desirable goal of therapy is to directly control PTH secretion. In recent case reports, anti-PTH immunotherapy showed promise (7, 8). Dendritic cell vaccination may also be applicable to induce a T cell immune response (9). Yet another approach is to target the parathyroid cell calcium-sensing receptor, which recognizes calcium as its cognate ligand (10) and is the principal regulator of PTH secretion.

Calcimimetics, allosteric modulators of the calcium-sensing receptor, directly reduce parathyroid cell hormone secretion by binding to the calcium-sensing receptor on parathyroid cells, increasing their sensitivity to extracellular calcium (11). A first-generation calcimimetic, R-568, controlled hypercalcemia for nearly 2 yr in a patient with widely metastatic parathyroid cancer (12). R-568 has been replaced by cinacalcet HCl (hereafter cinacalcet), a more potent second-generation agent with a longer half-life. In benign primary hyperparathyroidism, cinacalcet normalized serum calcium and reduced PTH concentrations for up to 3 yr (13, 14). Reported here are the results of the first multicenter investigation of cinacalcet in patients with inoperable parathyroid carcinoma.

Patients and Methods

Patients

The study was conducted at 15 centers in the United States and Europe. Twenty-nine patients (15 men, 14 women; 24–79 yr) with para-

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Abbreviations: BID, Twice daily; BSAP, bone-specific alkaline phosphatase; CV, coefficient of variation; NTx, N-telopeptide; QID, four times daily; TID, three times daily.

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thyroid cancer documented by histopathological examination of surgical specimens were enrolled. Exclusion criteria were any other malignancy (excluding nonmelanomatous skin cancers or *in situ* cervical cancer), concurrent cancer chemotherapy, non-parathyroid malignancy-associated hypercalcemia, and use of drugs metabolized by cytochrome P450 2D6 (inhibited by cinacalcet) with a narrow therapeutic index (flecanide, thioridazine, and tricyclic antidepressants).

Study protocol

This was a multicenter, open-label, single-arm, dose-titration study. Ethical considerations precluded a control group not receiving study drug. The study design included a variable-length titration phase (2–16 wk) and a maintenance phase. Study visits occurred weekly during the titration phase and every 8 wk during the maintenance phase. Patients initially received 30 mg cinacalcet twice daily (BID). Doses were increased every 2 wk for 16 wk, depending on the patient's serum calcium level and tolerance. Dose titration ceased when serum calcium concentration was 10 mg/dl or less, the dose reached 90 mg four times daily (QID), or the patient experienced an adverse event that precluded further increases (Fig. 1). Dose increases were permitted during the maintenance phase using the above sequence. Investigators were permitted to prescribe treatments deemed necessary to provide adequate supportive care.

The primary endpoint of the study was the proportion of patients experiencing at least a 1 mg/dl reduction in serum calcium from baseline at the end of the titration phase. The end of the titration phase could have occurred at any time between study wk 2 and 16, depending on the individual response of each patient. With baseline serum calcium levels of approximately 13–14 mg/dl, a level where most patients are symptomatic, we expected that a reduction in serum calcium of more than 1 mg/dl would be associated with an observable reduction in hypercalcemic symptoms. Secondary efficacy endpoints included changes from baseline in serum calcium, plasma PTH, serum N-telopeptide (NTx), and bone-specific alkaline phosphatase (BSAP) activity. Adverse events were recorded throughout the study.

Biochemical determinations

Serum samples were obtained for measurement of calcium and bone turnover markers after an overnight fast and before the morning dose of study drug (baseline and end of titration phase). Plasma samples were obtained at these time points to measure PTH. Fasting serum calcium levels were determined weekly during the titration phase. At d 1 and at the end of the titration phase, PTH and serum calcium were obtained before dose and 2 and 4 h after dose. Serum calcium and PTH were assessed every 8 wk during the maintenance phase, and bone turnover markers were assessed every 16 wk. Baseline and end of titration phase values were used to calculate the primary endpoint.

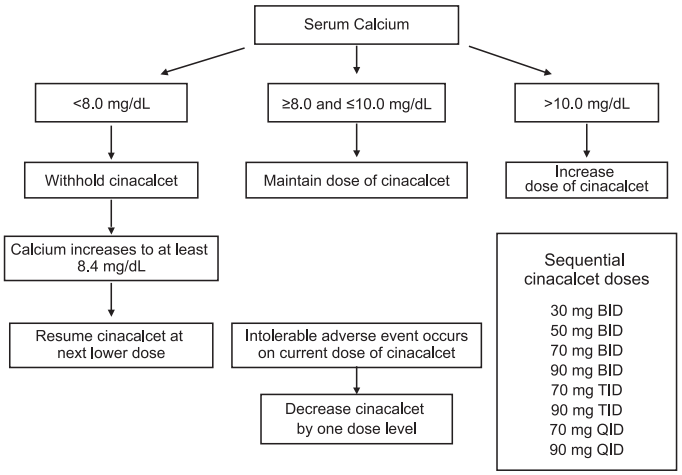

FIG. 1. Algorithm for dosing regimen. During the study, new formulation and dosage strengths of cinacalcet (30, 60, and 90 mg) were manufactured. Patients on either 50- or 70-mg dosage strengths were switched to a 60-mg dosage strength. Thus, patients receiving 50 mg BID and 70 mg BID were changed to 60 mg BID, patients receiving 70 mg TID were changed to 60 mg TID, and patients receiving 70 mg QID were changed to 60 mg QID.

All biochemical measurements, except for bone turnover markers, were performed at Covance Central Laboratory Services (Indianapolis, IN). Serum calcium was measured by standard methods [coefficient of variation (CV) = 1.4–1.5%). PTH was measured using an immunoradiometric assay (CV = 4.2–6.4%) (Allegro PTH; Nichols Institute Diagnostics, San Juan Capistrano, CA). Bone turnover markers NTx (Osteomark NTx assay; Ostex International, Seattle, WA; CV = 6.4–9.5%) and BSAP (Endocrine Sciences, Calabasas, CA; CV = 9.9–11.4%) were analyzed by ELISA.

Quality of life assessment

Health-related quality of life was assessed by means of a questionnaire at baseline and at the end of the titration phase. The questionnaire included the SF-36 (physical and emotional functioning) and MOS (cognitive functioning) rating scales (15, 16).

Statistical analysis

Safety and efficacy analyses are based on all patients enrolled in the study. The primary analysis was performed using data obtained at baseline and the end of the titration phase, which varied by patient between wk 2 and 16. Descriptive statistics are provided for clinical effects, bone turnover markers, and safety. Continuous variables are summarized using number of patients and mean ± SE, unless otherwise specified. Discrete variables are summarized using number and percentage. To assess changes in serum calcium by baseline level, patients were divided into three tertiles (serum calcium ≤13.3 mg/dl, >13.3 to <14.3 mg/dl, and ≥14.3 mg/dl). A Jonckheere-Terpstra test was used to assess the significance of the observed trend of larger calcium reductions associated with increasing baseline calcium. Two-tailed *t* tests were used to assess the percent changes from baseline for key laboratory parameters; a two-tailed paired *t* test was used to assess changes in health-related quality of life.

The study was designed by the investigators and Amgen Inc.; it was approved by the institutional review board at each study site and was conducted in accordance with the guidelines set forth in the Declaration of Helsinki. Each patient gave written informed consent. Statistical analyses were conducted at Amgen Inc. Data were interpreted by the investigators, who had full access to the primary data, participated in the statistical analyses, and were not limited with regard to statements made in this report. The lead investigators (S.J.S., D.M.S., M.P., M.R.R., and J.P.B.) were responsible for writing the article. Editorial assistance was provided by Amgen Inc. and was conducted in collaboration with all of the authors.

Results

Demographics and baseline characteristics

Patient demographics and baseline laboratory values are presented in Tables 1 and 2. All patients had recurrent disease after at least one parathyroid operation. Metastatic disease outside the neck was confirmed in 11 patients (lung and mediastinum most common) with bony metastases documented in only one individual. Serum calcium and PTH

TABLE 1. Baseline demographics of parathyroid carcinoma patients (n = 29)

Parameter	No. of patients or mean ± SE
Sex, men/women	15/14
Race, Caucasian/African-American	28/1
Age, mean yr ± SE (range)	51.0 ± 2.7 (24–79)
Prior parathyroid surgery	29
Kidney stone history	14
Prior bisphosphonate use	23
Fracture history	8

TABLE 2. Baseline biochemical data of parathyroid carcinoma patients (n = 29)

Parameter	Mean ± SE (range)	Normal range
Serum calcium (mg/dl)	14.1 ± 0.4 (8.6–20.2)[a]	8.4–10.3
PTH (pg/ml)	697 ± 94 (133–2106)	10–65
Serum phosphorus (mg/dl)	2.4 ± 0.1 (1.1–4.0)	2.2–5.1
Serum creatinine (mg/dl)	1.1 ± 0.1 (0.5–2.1)	Men, 0.5–1.2; women, 0.4–1.1
Serum albumin (g/dl)	3.9 ± 0.1 (2.0–5.1)	3.5–5.0
Total alkaline phosphatase (U/liter)	191 ± 24.5 (46–480)	35–115
BSAP (ng/ml)	72.6 ± 20.6 (7.1–588)	3.0–20.9
Serum NTx (nM BCE)	110.3 ± 26.7 (8–560)	5.4–24.2

BCE, Bone collagen equivalents.
[a] Two patients had normal serum calcium at study initiation, one after treatment with iv bisphosphonates for severe hypercalcemia.

levels were markedly elevated in all except two patients, one of whom received bisphosphonates for severe hypercalcemia immediately before study entry. Bisphosphonates had previously been used to control hypercalcemia in 23 of 29 patients. Mean serum phosphorus was in the low-normal range, and mean BSAP and NTx levels were elevated. As expected, patients had significant comorbidities associated with their advanced disease and uncontrolled hypercalcemia; complications included pathological fractures, renal insufficiency, renal stones, and hypercalcemic symptoms (somnolence, nausea, vomiting, decreased appetite, fatigue, and depression).

Patient disposition

All 29 patients received at least one dose of cinalcalcet. Nineteen patients completed the titration phase and entered the maintenance phase of the study. Ultimately, 23 patients did stop the drug because of nausea (one patient), nausea/vomiting (two patients), hives (one patient), investigator decision (three patients), consent withdrawn (three patients), lost to follow-up (three patients), hypercalcemia/hypokalemia (one patient), protocol deviation (one patient), noncompliance (three patients), and death (five patients). Seven patients died during the study or within 30 d of study withdrawal, due to cardiac arrest (two patients), congestive heart failure (one patient), hypotension (one patient), multiorgan failure (one patient), gastrointestinal hemorrhage (one patient), and worsening lung metastasis (one patient). Treatment duration ranged from 1–1051 d [mean ± SD, 328 ± 306 d; median (interquartile range), 229 (70–513) d].

Dosing information was collected for all patients either at the end of the titration phase or during the maintenance phase. The final dose distribution of patients at the time of their last study visit was 30 mg BID (three), 50/60/70 mg BID (three), 90 mg BID (two), 70 mg three times daily (TID) (four), 90 mg TID (three), 70 mg QID (one), and 90 mg QID (13).

Changes in serum calcium

By the end of the titration phase, serum calcium fell by at least 1 mg/dl in 62% of patients. In the group as a whole, mean calcium concentrations declined from 14.1 ± 0.4 mg/dl at baseline to 12.4 ± 0.5 mg/dl ($P = 0.049$; Fig. 2A). In the 18 patients who responded to cinacalcet with more than 1 mg/dl decline, serum calcium fell from 15.0 ± 0.5 to 11.2 ± 0.3 mg/dl ($P < 0.001$; Fig. 2B). In addition, there were 10 subjects who had sustained declines in serum calcium concentration. In these patients, the last serum calcium measured in the maintenance phase (on drug for 80 ± 12 wk; range, 33–151 wk) showed a decline from a baseline value of 15.4 ± 0.6 to 10.9 ± 0.3 mg/dl.

In some patients, the treatment target was achieved before the end of the titration period. The average reduction in all patients across the cinacalcet dose range was 1.7 mg/dl. Mean (SE) serum calcium concentrations by titration phase

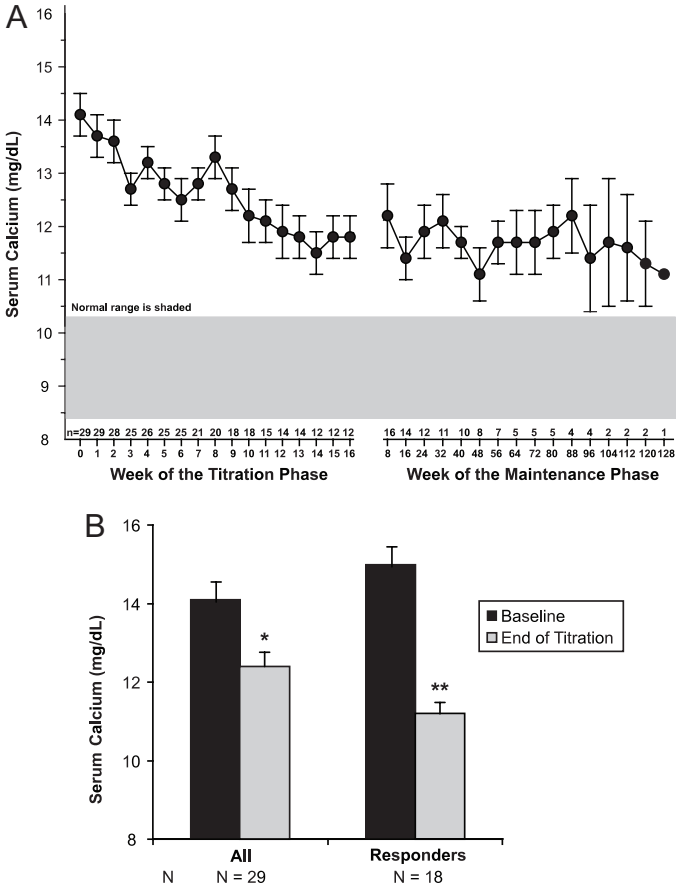

FIG. 2. A, Mean (± SE) predose serum calcium (milligrams per deciliter) throughout the titration and maintenance phases. Note that wk 16 of the titration phase does not represent the end of the titration phase for all patients. By study design, the end of dose titration was not based on a specific week. As noted in the text, 18 patients received at least 16 wk of cinacalcet treatment. B, Decline in serum calcium concentration during titration phase in parathyroid cancer patients treated with cinacalcet. Data (mean ± SE) are presented for all patients and for drug responders (who experienced a decline of ≥1 mg/dl in serum calcium levels). Decline in serum calcium was significant by paired *t* test: *, $P < 0.05$; **, $P < 0.001$.

and maintenance phase study week are shown in Fig. 2A. The greatest reductions in serum calcium were observed in patients with the highest baseline levels. The percent fall in serum calcium in the highest baseline calcium tertile was −25.0% *vs.* a change of +5.60% in the lowest baseline calcium tertile (Fig. 3). Eight patients in the group with the highest baseline serum calcium concentrations (≥14.3 mg/dl) had the greatest response to cinacalcet (17.9–10.4, 17.8–11.0, 20.2–14.3, 17.7–12.4, 15.9–10.8, 15.1–10.5, 14.4–10.7, and 14.3–9.7 mg/dl). However, the absolute level to which the serum calcium declined at the end of the titration phase was similar, regardless of baseline calcium tertile (lowest, 12.6 ± 0.9 mg/dl; middle, 12.4 ± 0.8 mg/dl; highest, 12.1 ± 0.8 mg/dl). For the 18 patients who remained on study for at least 16 wk, 17 (94%) had serum calcium values that were at least 1 mg/dl lower than at baseline at wk 16; the mean reduction for these patients was 3.8 mg/dl. In six patients, serum calcium increased by at least 1 mg/dl at the end of the titration phase. These patients were enrolled in the study for a relatively short duration (≤14 wk), primarily because of study drug intolerance. Adverse events of drug-related nausea and/or vomiting were documented for each of these patients, which may have led to a lack of study drug compliance or inability to absorb study drug after ingestion. Individual responses to cinacalcet along with the dosing range and duration on study are presented in Fig. 4.

Changes in calciotropic parameters

Mean PTH levels were markedly elevated at baseline (697 ± 94 pg/ml) and decreased to 635 ± 73 pg/ml by the end of titration. The mean percent change in PTH was −4.6% ($P = 0.549$). As shown in Fig. 5, PTH levels on d 1 decreased within 4 h (predose, 697 ± 94 pg/ml; 2 h, 654 ± 97 pg/ml; 4 h, 661 ± 95 pg/ml); the mean percent change was −12.4%

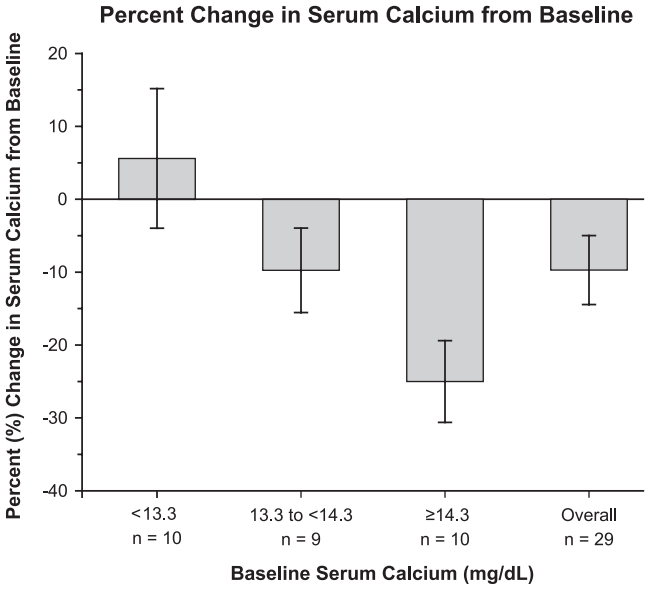

FIG. 3. Percent change (± SE) in serum calcium at the end of the titration phase as a function of the baseline calcium level. A Jonckheere-Terpstra test showed that the decrement in serum calcium concentration among the tertiles of serum calcium concentration at baseline significantly differed from one another ($P = 0.002$).

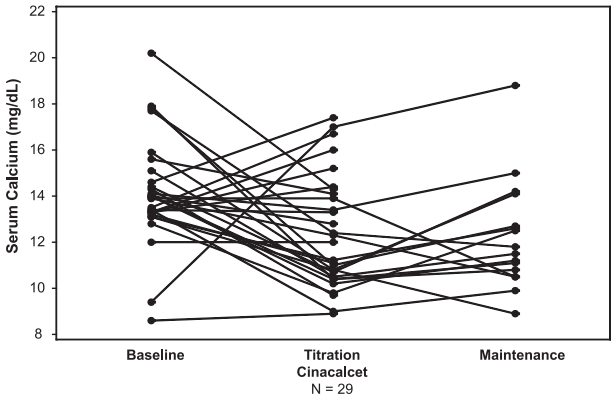

FIG. 4. Individual serum calcium levels for each patient at baseline, end of titration, and maintenance phase. The last weekly measurement from each phase was taken. Note that the doses at the end of titration phase ranged from 30 mg BID to 90 mg QID; doses at the end of the maintenance phase ranged from 70 mg TID to 90 mg QID. The duration of treatment on study for all patients ranged from 1–151 wk.

at 4 h after dose ($P < 0.001$). Similar decreases in PTH were observed at the end of dose titration (predose, 635 ± 73 pg/ml; 2 h, 576 ± 68 pg/ml; 4 h, 555 ± 60 pg/ml); the mean percent change was −7.7% ($P = 0.009$). These decreases in PTH corresponded with postdose increases in plasma cinacalcet concentrations (data not shown).

Serum phosphorus concentrations remained within the normal range, increasing from 2.4 ± 0.1 mg/dl at baseline to 3.0 ± 0.2 mg/dl ($P = 0.016$) at the end of the titration period.

Bone turnover markers were elevated at baseline [BSAP: mean 72.6, median 37.0 (normal range, 3.0–20.9) ng/ml; serum NTx: mean 110.3, median 50.0 (normal range, 5.4–24.2) nM]. By the end of the titration phase, both markers had increased, BSAP by 103% (median 37.2%) ($P = 0.010$) and serum NTx levels by 49.3% (median 30.3%) ($P = 0.029$).

Health-related quality of life

The questionnaire was completed by 28 patients at baseline and by 15 patients (54%) at the end of the titration phase. Consistent with the disease severity in this population, patients tended to score in the lower half of the standard range.

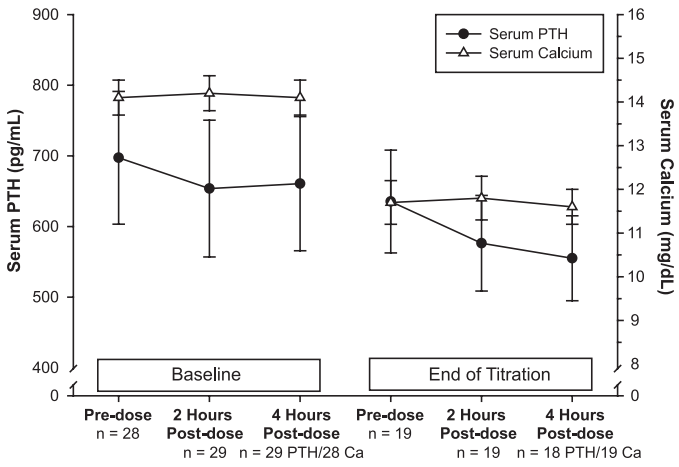

FIG. 5. Change in PTH and serum calcium after dosing at baseline and after dosing at the end of the titration phase.

None of the parameters demonstrated statistically significant changes.

Adverse events

The most common adverse events were nausea (66%), vomiting (52%), dehydration (24%), and headache (21%). The most frequently occurring serious adverse events were fracture (21%) and hypercalcemia (21%). In five patients, adverse events [nausea/vomiting (two), nausea (one), hives (one), and hypercalcemia (one)] were considered to be treatment related and resulted in withdrawal from the study. Seven patients died during the study or within 30 d of study drug withdrawal. None of the deaths were considered treatment related.

Six of 29 patients (21%) experienced a fracture (hip/femoral or neck/intratrochanteric) between wk 5 and 69 of the study. Two of the six patients had a history of previous hip fracture before enrolling in the study. Of the six patients who experienced fractures during the study, two patients had more than one fracture. In these patients, the other fractures were of the arm (both patients) and a cervical compression (one patient). The fractures were considered related to the underlying disease and not to cinacalcet treatment.

Discussion

The symptoms associated with metastatic parathyroid carcinoma are typically due to hypercalcemia rather than tumor invasion. Because the main cause of morbidity is hypercalcemia, lowering serum calcium often results in clinical improvement. With approximately 50% of all parathyroid cancer patients surviving more than 10 yr after diagnosis (12), the need for a therapy that provides continuous and adequate control of hypercalcemia at nonsymptomatic levels is clear. However, treatment options for refractory disease have been limited; chemotherapy and radiotherapy are ineffective. Medical approaches to hypercalcemia in this disease are also limited. Calcitonin in combination with glucocorticoids may be useful for acute hypercalcemia but have limited effect after several days (17). Oral bisphosphonates are ineffective, and the improvement with iv administration is transient (18–20). Calcimimetics are attractive to consider because they reduce PTH synthesis and secretion and lower serum calcium levels (21, 22). In this study, cinacalcet was effective in lowering serum calcium and maintaining these levels in patients with metastatic parathyroid carcinoma.

Two thirds of the inoperable parathyroid cancer patients in this study demonstrated reductions in serum calcium after treatment with cinacalcet. Dramatic reductions (>5 mg/dl) in serum calcium were observed in the most severely hypercalcemic patients, supporting the ability of cinacalcet to control hypercalcemia in those with greatest need. Consistent with the study design, patients with higher baseline serum calcium concentrations were titrated to higher doses of cinacalcet, a point that underscores its efficacy in severely hypercalcemic patients. The sustained reductions in serum calcium concentration suggest that cinacalcet can be used chronically for treatment of hypercalcemia. The results also demonstrate that some patients with parathyroid cancer can tolerate cinacalcet at significantly higher doses (up to 90 mg QID) than those tested in previous studies of benign primary hyperparathyroid disease. Unlike other treatment options for parathyroid cancer, cinacalcet can be used in patients with renal insufficiency, a common comorbidity of longstanding severe hyperparathyroidism (23). In fact, the drug has been approved for use in patients on dialysis. Quality of life data are difficult to interpret because only 54% of patients completed the follow-up questionnaire.

The substantial decline in serum calcium levels appears out of proportion to the modest 4.6% reduction in PTH levels. The suppression of PTH concentrations after dosing with cinacalcet is time dependent both in patients with primary and secondary hyperparathyroidism or renal disease and, as shown in this study, in patients with parathyroid cancer. Reductions in PTH are inversely correlated with cinacalcet plasma concentrations. After a dose of cinacalcet, plasma concentrations reach peak levels 2–4 h after dosing, which corresponds to the nadir for PTH (14, 24). It is possible that the physiological relationship between PTH and calcium is altered in parathyroid carcinoma, with an increase in the insuppressible fraction of PTH secretion. It is also possible that parathyroid cancer cells produce an immunoreactive but biologically inactive fragment or that these cells lack sufficient numbers of calcium-sensing receptors coupled effectively to the mechanisms that regulate PTH secretion. In addition, direct actions of cinacalcet on the calcium-sensing receptor in the kidney or on bone may be involved; urinary calcium excretion or bone mineral density in response to drug was not measured. Although no changes in these parameters were observed during a 1-yr study of cinacalcet treatment in benign primary hyperparathyroidism, fractional urinary excretion of calcium did decline (12). Markers of bone resorption and formation increased above the already elevated baseline levels, an effect also reported in benign primary hyperparathyroidism (12). The reason for this is not clear; fluctuations in PTH or a direct effect on bone that is independent of PTH are potential mechanisms. Finally, perhaps a change in PTH secretory dynamics, however modest, is sufficient to shift the balance of bone turnover more toward bone formation relative to bone resorption in these patients. Additional studies will be required to address these possibilities.

The high withdrawal rate and serious adverse events of death and fracture in this study were not unexpected because patients had advanced and incurable disease and, in many cases, were followed for a relatively long period of time, allowing for progression of the underlying disease and associated comorbidities. Six patients had serum calcium increases of at least 1 mg/dl from baseline to the end of titration phase. These patients were on study for no longer than 14 wk, and their compliance with the drug regimen may have been limited by side effects of cinacalcet. Furthermore, it is difficult to know in these patients whether these increases would have been even greater without the use of cinacalcet, because a control group was considered unethical for this study. Although there are no data in humans on the effect of cinacalcet on tumor growth, it is unlikely that cinacalcet worsened the underlying disease. Calcimimetic compounds have been shown to attenuate parathyroid gland cell proliferation in animal models of secondary hyperparathyroidism, in part due to increased expression of the endogenous cyclin-dependent kinase inhibitor p21 (25, 26).

In summary, cinacalcet significantly reduced hypercalcemia in a sustained manner in patients with parathyroid cancer. These data suggest that treatment can be initiated in the short

term when hypercalcemia persists and after surgical approaches to the disease are no longer indicated or feasible. Cinacalcet is also likely to have a role in the chronic management of intractable hypercalcemia due to parathyroid cancer. Although ethical considerations limited the study design, this report provides clear proof of concept that cinacalcet successfully lowers serum calcium in many patients with inoperable parathyroid cancer, and that cumulative doses up to 360 mg/d (90 mg QID) are generally well tolerated. Because of its novel mechanism of action and the relatively well-tolerated administration demonstrated in this study and in clinical trials in patients with renal disease (27–29) and primary hyperparathyroidism (14, 30), cinacalcet offers important benefits in the treatment of hypercalcemia in patients with parathyroid cancer.

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