Case Report

Cinacalcet for the Treatment of Humoral Hypercalcemia of Malignancy: An Introductory Case Report with a Pathophysiologic and Therapeutic Review

Michael Sheehan^a Sabo Tanimu^b Yusuf Tanimu^c Jessica Engel^d
Adedayo Onitilo^d

^aDepartment of Endocrinology, Marshfield Medical Center – Weston, Weston, WI, USA;

^bDepartment of Gastroenterology, Marshfield Medical Center – Weston, Weston, WI, USA;

^cDepartment of Internal Medicine, Marshfield Medical Center – Marshfield, Marshfield, WI,

USA; ^dDepartment of Oncology, Marshfield Medical Center – Weston, Weston, WI, USA

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Abstract

Hypercalcemia is an ominous development in the course of malignancy associated with a mean survival of only several months. A majority of cases of hypercalcemia are related to humoral hypercalcemia of malignancy (HHM), where hypercalcemia is caused by increased levels of circulating parathyroid hormone-related protein (PTHrP). Mainstay treatments in the management of HHM are intravenous fluids, intravenous bisphosphonates, and subcutaneous denosumab, although hypercalcemia oftentimes recurs despite these efforts. We present a case of advanced non-small cell lung cancer with PTHrP-mediated hypercalcemia that proved resistant to standard therapy. A trial of oral cinacalcet was initiated and improved calcium levels for 2 months despite a progressive rise in PTHrP and prior to subsequent disease progression. Based on the current body of literature, we propose that this calcium-lowering effect of cinacalcet occurs due to a potential effect on renal calcium excretion.

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Introduction

Hypercalcemia of malignancy (HCM) is most commonly mediated by parathyroid hormone-related protein (PTHrP), wherein it is referred to as humoral HCM (HHM). The development of HHM is an ominous sign in the course of malignancy, where the mean survival after development

Michael Sheehan, MD
Department of Endocrinology
Marshfield Medical Center – Weston, 3501 Cranberry Blvd
Weston, WI 54476 (USA)
sheehan.michael@marshfieldclinic.org

of hypercalcemia is between 2 and 3 months and is often related to progression of the underlying malignancy [1]. Acute symptoms of HHM are generally managed with intravenous (IV) fluids, IV bisphosphonates (BPs), and subcutaneous calcitonin [1, 2]. Chronically, intermittent administration of IV BPs and/or subcutaneous denosumab on an outpatient basis are often used to manage HHM [1, 2]. Despite initial success in treating hypercalcemia through these means, the patient's underlying malignancy often progresses. It is important to note that standard regimens of BPs and denosumab therapy exclusively affect skeletal calcium metabolism as a means of controlling hypercalcemia of HHM [1, 2]. As such, it may be possible to improve the management of HHM by using a therapy that increases renal calcium excretion.

We report a case of recalcitrant HHM in a patient with advanced non-small cell lung cancer (NSCLC) that responded to cinacalcet treatment. We propose a mechanism of action for this effect.

Case Report

An 81-year-old female with NSCLC and a previous history of recurrent stage I bladder cancer exhibited symptoms corresponding to elevated calcium levels. She had previously been diagnosed and treated with chemoradiation for NSCLC in 2016 and been found to have disease progression with an enlarging lung mass in early 2018. An IV regimen of 240 mg nivolumab administered every 2 weeks was initiated for treatment in 2018; the patient received 2 doses before the dose was changed to 480 mg monthly for 2 doses. She developed mild hypercalcemia 5 weeks later (10.6 mg/dL; normal range: 8.5–10.1).

In spring of 2018, she was admitted to the hospital with fatigue, progressive lower extremity weakness, appetite loss, and confusion. Computed tomography (CT) of the head was negative for intracranial metastasis. Her total calcium and ionized calcium levels were elevated at 12.7 mg/dL and 6.9 mg/dL (normal range: 4.6–5.4), respectively. Parathyroid hormone (PTH) was suppressed at <6 pg/mL (normal range: 18–85), and PTHrP was mildly elevated at 3.3 pmol/L (normal range: 0–2.0).

She was treated with IV fluids and pamidronate (Table 1). Her calcium levels decreased to 8.2 mg/dL (total) and 5.2 mg/dL (ionized) 4 days later. Unfortunately, 3 weeks later, she was readmitted with increasing weakness and confusion, and her calcium levels were again elevated at 11.1 mg/dL (total) and 6.3 mg/dL (ionized). Her intact PTH level was low at 5.8 pg/mL, but PTHrP was now very elevated at 41.9 pmol/L. She received IV fluids and, on this occasion, zoledronic acid (ZA), after which her total calcium decreased to 8.7 mg/dL within 2 days. However, 3 days later, her calcium levels were back up to a high normal at 10.1 mg/dL, and she was given a subcutaneous dose of denosumab. Despite this, in another 3 days, she required readmission to the hospital with her total calcium level again high at 11.1 mg/dL. Her total calcium level normalized to 9.0 mg/dL after an additional dose of ZA and 2 doses of subcutaneous calcitonin, though her ionized calcium remained mildly elevated at 5.4 mg/dL.

Because of this persistently difficult-to-control hypercalcemia, she was started on an oral regimen of 30 mg cinacalcet twice daily. Her calcium levels improved initially, only to rise slightly, necessitating an increase in cinacalcet dose (Table 1). For approximately 2 months, her calcium levels remained normal, if not occasionally low, despite a persistent PTHrP elevation to between 143 and 194 pmol/L. No further BP or denosumab therapy was required.

A follow-up chest CT was notable for progression of the lung lesion and development of a new liver lesion. Nivolumab was discontinued for concern of progression of the primary disease, and 2 months later, a follow-up chest CT showed continued progression of the NSCLC. The patient opted to proceed with hospice care and died about 5 weeks later without further laboratory results being obtained.

Table 1. Laboratory data

Date	Total Ca ²⁺ , mg/dL	Ionized Ca ²⁺ , mg/dL	PTH, pg/mL	PTHrP, pmol/L	Treatment
Onset of hypercalcemia (day 1)	10.6 ^a				
Day 25	12.7 ^a	6.9 ^c	<6.0 (nl: 18–85)	3.3 ^e	Pamidronate 60 mg IV
Day 29	8.2 [#]	5.2 ^c			
Day 42	11.1 [#]	6.3 ^d	5.8 (nl: 18.4–80.1)	41.9 ^f	Zoledronic acid 2 mg IV
Day 43	9.2 [#]	5.6 ^d			
Day 44	8.7 [#]				
Day 47	10.1 ^a				Denosumab 120 mg subQ
Day 50	11.1 ^a	6.6 ^c			Zoledronic acid 2 mg IV + calcitonin 200 IU subQ × 2 doses
Day 51	10.6 ^a	6.2 ^c			
Day 53	9.6 ^a	5.6 ^c			
Day 54	9.0 ^a	5.4 ^c			
Day 57	10.1 ^b				
Day 58		6.0 ^d			Cinacalcet 30 mg PO b.i.d.
Day 61	8.9 ^a	5.5 ^d			
Day 70	9.4 ^b	5.1 ^d			
Day 76	10.1 ^b	5.7 ^d		113 ^f	Cinacalcet 60 mg PO b.i.d.
Day 82	9.4 ^b	5.4 ^d			
Day 89	8.9 ^b	4.9 ^d		194 ^f	
Day 96	7.3 ^b				
Day 103	8.8 ^b	4.9 ^d			
Day 110	8.5 ^b	4.7 ^d			
Day 117	8.2 ^b	4.6 ^d		143 ^f	

Normal range key: ^a 8.2–10.0; ^b 8.5–10.1; ^c 4.5–5.3; ^d 4.6–5.4; ^e <2.0; and ^f 0.0–3.4. b.i.d., administered twice daily; IU, international units; IV, intravenous; nl, normal level; PO, oral administration; subQ, subcutaneous.

Discussion

Our patient had HHM related to NSCLC, a classic malignancy for this etiology of HCM [1, 2]. Her PTHrP was initially just mildly elevated, but with disease progression, it rose substantially. Though she had responded to IV BP therapy initially, recurrence of hypercalcemia was resistant to BP in combination with denosumab. This lack of response was likely due to disease progression, noted by the rising PTHrP level. As standard therapy only affects the action of PTHrP in the skeleton, we attempted a therapy we thought would affect the action of PTHrP in the kidneys, hoping to increase renal calcium excretion to help manage HHM. Since cinacalcet affects the calcium-sensing receptor (CaSR) in the distal nephron, we thought it might be a viable option [3–6].

As shown, our patient *did* respond to cinacalcet treatment. We are aware of only 3 similar cases previously reported in the literature [2, 7, 8]. Our patient's response persisted even in the face of disease progression, marked by a further rise in PTHrP. In retrospect, it would have been helpful to measure this patient's fractional excretion of calcium both before and at various times during cinacalcet therapy; unfortunately, such measurements were not obtained. Despite the lack of these calcium excretion measurements, we believe an understanding of renal calcium excretion and its various controllers supports our proposed mechanism of action.

Fig. 1. Normal calcium homeostasis (**A**) and abnormal calcium homeostasis (**B**) in humoral hypercalcemia of malignancy. **A** If/when extracellular calcium ($\text{Ca}^{2+}[\text{e}]$) decreases (**A**), the calcium-sensing receptor (CaSR) on the parathyroid C cells is inhibited, resulting in increased parathyroid hormone (PTH) secretion (**B**). Increased PTH acts in the bones and kidneys. The effect of PTH in bone increases osteoclast (OC) function (**C**). In the kidneys, PTH increases calcium reabsorption in the distal convoluted tubule (**D**). In addition, PTH increases the activity of 1- α -hydroxylase in the kidneys (**E**), which in turn increases 1,25-OH vitamin D, thus increasing calcium absorption from the intestines (**F**). All of these mechanisms are designed to restore/maintain normal serum calcium levels. **B** PTH-related protein (PTHrP) is secreted by malignant cells (**A**). Because of its homology with PTH, it interacts with the PTH receptor (PTH-1r) in the bones and kidneys, resulting in increased bone resorption (**B**) and increased calcium reabsorption (**C**), respectively. This, in turn, raises extracellular calcium (**D**), which stimulates CaSR (**E**), resulting in lower PTH levels (**F**) [1–4, 9, 13].

Normal Calcium Homeostasis

The human body contains ~1,000 g (10^6 mg) of calcium, 99.9% of which is bound in skeletal hydroxyapatite, of which ~275 mg (<0.03%) is turned over daily. The extracellular space contains ~1,000 mg of calcium (~650 mg in the interstitial space and ~350 mg in the plasma). Intracellular calcium makes up the smallest portion at <0.1 mg. Generally, the human body is in a state of net calcium balance. We ingest ~1,000 mg daily, of which ~500 mg is absorbed. Calcium is secreted by the intestines at a rate of ~325 mg daily, however, resulting in a net absorption of ~175 mg [1]. The kidneys filter ~10,000 mg of calcium daily, but they reabsorb 97–99% of that amount, thus excreting only ~200 mg per day [3].

The net balance of calcium is therefore maintained with intestinal absorption approximately equaling renal excretion [1]. In the context of our case, it is important to note that normal calcium turnover in bone is ~275 mg, whereas normal calcium filtration/reabsorption in the kidneys is >35 times that amount (~10,000 mg). This highlights the potential importance of renal mechanisms, not only in the pathophysiology of HHM, but also in its treatment.

PTH and Calcium Homeostasis

PTH is the primary regulator of calcium homeostasis in the human body (Fig. 1). Its secretion is regulated in a reciprocal fashion by plasma calcium itself via CaSR on the surface of parathyroid chief cells, although CaSR is also located in other tissues, most notably in bone and at various sites along the nephron. PTH is involved in all three aspects of calcium metabolism via its action at the PTH-1 receptor: bone turnover, intestinal calcium absorption, and renal reabsorption of calcium. The action of PTH in bone involves its binding to receptors on osteoblasts, which leads to increased secretion of receptor activator of nuclear factor kappa-B ligand (RANKL), which in turn binds to RANK on osteoclasts, increasing their number and function [9]. This resorption of bone leads to calcium efflux (Fig. 2). Renal reabsorption of

Fig. 2. Effect of parathyroid hormone (PTH), PTH-related protein (PTHrP), bisphosphonates (BPs), and denosumab on bone metabolism. PTH and/or PTHrP bind to the PTH-1r receptor on osteoblasts (A), increasing the production of RANKL (B). RANKL binds to RANK receptors on osteoclasts (C), activating bone resorption, leading to calcium efflux into the extracellular space (D). Denosumab inhibits this process by binding to RANKL to prevent its binding to the RANK receptor (E). BPs in the bone matrix directly inhibit osteoclast function (F). Both of these actions decrease calcium efflux into the extracellular space [1, 2, 9, 15, 16].

calcium is affected by PTH at the distal convoluted tubule via multiple steps, which ultimately results in active transcellular movement of calcium across the apical membrane through transient receptor potential vanilloid 5 (TRPV5) channels and reabsorption across the basolateral membrane [3] (Fig. 3A). The effect of PTH on gastrointestinal calcium absorption is indirect via stimulation of renal 1- α -hydroxylase increasing levels of active vitamin D (1,25-OH vitamin D) (Fig. 1A).

Normal Renal Calcium Handling

As mentioned, ~10,000 mg (equivalent to 1% of the total body calcium stores) is filtered by the kidneys daily, and ~98% is reabsorbed. Therefore, even relatively small changes in calcium reabsorption along the nephron may have significant effects on serum calcium levels. Most renal calcium reabsorption occurs passively and paracellularly in conjunction with sodium and water in the proximal tubule via the claudin-2 channel, which amounts to ~65% of total reabsorption (~6,500 mg daily) [3]. In the thick ascending loop of Henle, a further ~25% (~2,500 mg daily) is also reabsorbed passively and paracellularly via the claudin-16 channel [3]. Unlike in the proximal tubule, in the thick ascending loop of Henle, this process can be inhibited by CaSR via a series of complex steps that ultimately diminish the lumen-positive potential, thus preventing calcium reabsorption [3] (Fig. 3B). Lastly, the final ~10% (~1,000 mg daily) of calcium reabsorption occurs in the distal convoluted tubule via the TRPV5 channel and is also an active, transcellular process [3] (Fig. 3A).

Hypercalcemia itself induces increased calcium excretion via a decrease in PTH and decreased activation of CaSR in the nephron. The normal fractional excretion of calcium of ~2% was shown to increase to ~6.5% in normal subjects by increasing serum calcium from ~9.1 to ~10.2 mg/dL via a hypercalcemic calcium clamp [10]. Mechanistically, the activity of TRPV5 is inhibited by activation of CaSR [4]. CaSR knockout mice cannot increase urinary calcium excretion in response to a calcium load [5], while TRPV5 knockout mice exhibit a 6-fold increase in urinary calcium excretion compared to wild-type mice [11]. In humans, there are examples of activating mutations of CaSR that result in hypocalcemia and relative hypercalciuria; these patients generally exhibit moderately low serum calcium levels at ~7.0–8.0 mg/dL [12]. Overall, ~35% of renal calcium reabsorption is under partial inhibitory control by CaSR; hence, stimulation of CaSR could have profound effects on renal calcium excretion.

Fig. 3. Calcium handling in the distal convoluted tubule (**A**) and thick ascending loop of Henle (**B**). **A** In the distal convoluted tubule, parathyroid hormone (PTH) and PTH-related protein (PTHrP) promote the reabsorption of calcium via activation of the PTH-1r receptor on the luminal membrane. Calcium first enters from the lumen via the TRPV5 channel and is transported by calbindin-D28k to the basolateral membrane, where it is reabsorbed via activity of PMCA1b and NCX1. Activation of calcium-sensing receptor (CaSR) inhibits this process by inhibiting PMCA1b, the primary mechanism of calcium transport across the basolateral membrane. Additionally, activation of CaSR decreases the number of TRPV5 channels. **B** In the thick ascending loop of Henle, coordinated activity of the NKCC2, ROMK, CLCNKB, and Na-K ATPase channels leads to a lumen-positive potential, which in turn favors the reabsorption of Ca^{2+} via the claudin-16 channel. Activation of CaSR via several mechanisms inhibits the generation of this lumen-positive potential, thus leading to decreased calcium reabsorption and subsequently increased calcium excretion [3–6, 10, 11, 13, 14].

Abnormal Renal Calcium Handling Related to PTHrP

HHM is the most common etiology of malignancy-related calcium dysregulation and accounts for ~80% of HCM cases [1, 2]. Most often, it occurs in solid tumors of the lung, head and neck, esophagus, skin, cervix, breast, kidneys, prostate, and bladder [1, 2]. These patients do not have bone metastases, and hypercalcemia occurs via PTHrP actions in both the bones and kidneys [1, 2]. PTHrP has some homology with PTH, especially at the amino-terminus, and binds to the PTH-1 receptor, resulting in increased skeletal efflux of calcium and increased renal reabsorption of calcium by the mechanisms described earlier for PTH (Fig. 1A, 2, 3A).

The relative contribution of each of these processes to hypercalcemia is unknown, but it is estimated that up to 1,000 mg of calcium per day may be mobilized from the skeleton in HHM [2]. Additionally, there is an underappreciated renal contribution to HHM, as evidenced by studies in both animals and humans. In rats with HHM refractory to bone resorption inhibitors, anti-PTHrP antibodies resulted in a marked decrease in blood calcium coinciding with a 2- to 3-fold increase in fractional excretion of calcium [13]. Furthermore, in normal human subjects infused with PTHrP, the fractional excretion of calcium (control group: ~2%) increased by ~50% less (~2.5–3.7%) than the increase induced by a similar rise in serum

calcium via a calcium infusion (~6.5%) [10, 14]. Thus, PTHrP induces a *relative* (not absolute) hypocalciuria. That is, patients with HHM *will* increase urinary calcium excretion, but not to the degree they would have if it were not for the presence of PTHrP.

Treatment of HCM

Treatment of the underlying malignancy is of utmost importance in managing HHM. This is difficult, however, as evidenced by the very low mean survival rate among these patients. Beyond management of the malignancy itself, IV fluids, IV BPs, and subcutaneous denosumab have become standard treatments for HHM [1, 2]. It is important to understand the mechanism of action of these two agents and the potential of cinacalcet to act via a separate mechanism.

Intravenous BPs

Pamidronate and ZA are the most commonly used BPs for this purpose. The onset of action is generally 1–3 days, with the nadir in serum calcium occurring by day 4–7 and the duration of the effect being 1–3 weeks [1, 2]. Of these two agents, ZA has greater efficacy [15]. In a head-to-head study, ZA exhibited a greater complete response rate, rate of normalization of serum calcium, and duration of effect than pamidronate [15]. The mechanism by which BPs lower serum calcium in HHM is via several effects on both the number and function of osteoclasts, including decreased recruitment and development, increased apoptosis, and decreased attachment to binding sites on bone [1, 2]. The ability of BPs to influence serum calcium levels is related to their binding to hydroxyapatite in bone, thus being incorporated into the bone matrix itself [1, 2] (Fig. 2). There is no known effect of BPs on renal calcium handling.

Subcutaneous Denosumab

Denosumab is a human monoclonal antibody that binds RANKL, preventing its binding to the RANK receptor on osteoclasts, thereby decreasing bone resorption (Fig. 2). It was approved for use in HCM in 2014. Presently, it has become useful in BP-refractory HCM, as well as in prevention of HCM in patients with metastatic bone disease (osteolytic metastases) [16]. This is important, because ~22% of patients have an incomplete response to BPs, and an additional ~24% of patients relapse within 56 days of BP therapy [16]. Denosumab has no known effect on renal calcium handling.

Oral Cinacalcet

Cinacalcet was approved for use in parathyroid carcinoma in 2004. It acts as a calcimimetic, interacting with CaSR on parathyroid cells in a positive allosteric fashion to downregulate the release of PTH with a resultant decrease in serum calcium [2]. As mentioned previously, CaSR is also present in bone and renal tissue and, while there is still a relatively limited understanding of its direct role in bone metabolism [17], it plays an important role in renal calcium handling [3–6] (Fig. 3).

There are no clinical trials of cinacalcet in HCM beyond the setting of parathyroid carcinoma. In each of the 3 previously published cases involving a patient with HHM refractory to BP with or without denosumab therapy, calcium levels were successfully managed with cinacalcet, although the mechanism by which cinacalcet may have worked was not fully discussed even theoretically [2, 7, 8]. In one case, the authors considered the improvement to be related to a cinacalcet-induced decrease in PTHrP itself, although that effect was more likely the result of ongoing chemotherapy [7]. In another, no mechanism was postulated [2]. In the third case, the authors suggested the possible interaction of cinacalcet with CaSR in bone and/or the kidneys as the mechanism, but they did not elaborate this more fully [8].

In our view, this seems the most plausible mechanism, given the above-outlined importance of renal calcium reabsorption to overall calcium homeostasis and the significant effect

of alterations in CaSR expression on this process. Most notably, both in mouse knockout models of CaSR [5] and the TRPV5 channel [11] and in the rare familial hypocalciuric hypercalcemia (inactivating mutation of CaSR) [12], serum calcium levels are significantly altered by changes in renal calcium handling by this mechanism. Also, activating mutations of CaSR result in hypocalcemia, with serum calcium levels approximately 1.5 mg/dL below the mid-to-normal range [12].

Conclusion

Standard therapy for HHM has limited effectiveness over time in large part due to the progressive nature of the underlying malignancy. However, it is possible that a relative increase in renal calcium reabsorption by PTHrP is being overlooked by our current therapeutic approach to this condition. Based on our patient's response to cinacalcet treatment with respect to decreased calcium levels, we propose that cinacalcet may lower serum calcium in HHM via its effects on CaSR in the distal nephron to enhance renal calcium excretion. As such, increased use of this drug may be warranted in HHM unresponsive to standard therapies, and perhaps simultaneously along with those therapies earlier in the course of the disease. Lastly, if cinacalcet therapy is used for this purpose, measurement of the fractional excretion of calcium before and at various time points during therapy should be performed in an effort to document the potential renal mechanism of this treatment's calcium-lowering effect.

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Statement of Ethics

The authors acknowledge that the subject gave written informed consent to publish her case.

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All authors reviewed the medical records and data and participated in the writing of the paper.

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