THE UNIVERSITY OF CHICAGO
MEDICINE & BIOLOGICAL SCIENCES
AT THE FOREFRONT OF MEDICINE®

65 Y.o male with severe hypercalcemia

Endorama

January 2018

THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

AT THE FOREFRONT OF MEDICINE®

MALIGNANCY INDUCED HYPERCALCEMIA

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First year adult endocrine fellow

CME Text Code for Endorama

LOLQUK

I have no relevant financial relationships with any commercial interests

OBJECTIVES

- Signs, symptoms and the differential diagnosis of hypercalcemia
- Evaluation and management of hypercalcemia
- Review pathophysiology of cancer induced hypercalcemia
- Review the management of cancer-induced hypercalcemia

HPI

65 years old male with PMH of aortic regurgitation, A-Fib, HTN, SCC of the right foot

Consult: Hypercalcemia
CC: Increasing fatigue and palpitations

- Five days PTA, he was fatigued and tired upon walking
- SOB + palpitations on few occasions
- Complains of constant pain to his left neck and stiffness
- He endorses dysphagia and odynophagia with solid food and is only able to tolerate liquids
- ~ 10 lb weight loss over the past month
- He denies taking Ca or vitamins D supplements

MORE HISTORY

- He developed a R foot wound after stepping on a piece of glass in 2017. He had issues with wound healing c/b infections.
- Underwent debridement by podiatry and biopsy showed invasive squamous cell carcinoma (4/2018)
- At the time, the lesion was excised with femoral and inguinal lymph nodes.

HPI

PMH:
Aortic regurgitation
Atrial fibrillation
HTN
Squamous cell carcinoma (*R foot*)

PSH: Radical resection of R tumor, R inguinofemoral superficial lymphadenectomy
EP cardioversion

PFH: Diabetes Father
Cancer - Pancreatic Mother
Cancer - Breast Mother

SH: Former smoker, 1/2 PPD for 5 yrs

PTA Meds:

- Lipotor 40 mg
- Iron tablets
- Losartan 50 mg
- Toprol XL 100 mg
- Miralax
- Warfarin 2 mg

ROS

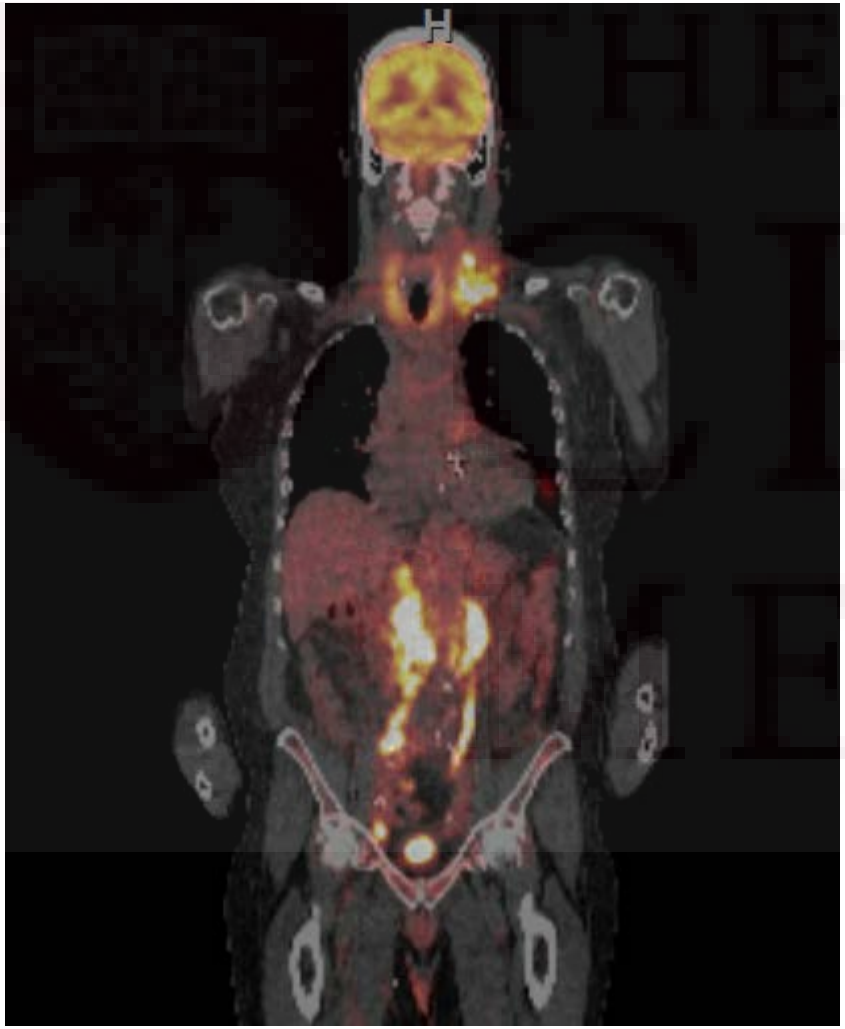
- Constitutional: Positive for malaise/fatigue. Negative for chills and fever
- HENT: Negative for ear discharge and hearing loss. Neck pain
- Eyes: Negative for blurred vision
- Respiratory: Negative for cough
- Cardiovascular: Negative for chest pain, + palpitations
- Gastrointestinal: Negative for abdominal pain, constipation, diarrhea, nausea and vomiting
- Genitourinary: Negative for dysuria and urgency
- Musculoskeletal: Positive for neck pain. Negative for back pain and falls
- Skin: Negative for rash
- Neurological: Negative for tremors and weakness
- Endo/Heme/Allergies: Negative for polydipsia
- Psychiatric/Behavioral: Negative for substance abuse and suicidal ideas
- All other systems reviewed and are negative

PHYSICAL EXAM

- BP 121/88 | **Pulse 99 |** Temp (97.5 °F) | Resp 17 | Ht (6' 3") | Wt 99.8 kg (220 lb) | SpO2 97% | BMI 27.5 kg/m2

- Constitutional: no acute distress
- HEENT: EOMI, oropharynx clear
- Neck: supple, no thyromegaly, **left large firm neck mass**
- Cardiovascular: **irregular** rate, no extra heart sounds
- Pulmonary/Chest: good respiratory effort, clear to auscultation bilaterally
- Abdomen: bowel sounds present, soft, non-tender, no violaceous straie
- Musculoskeletal: moving all extremities, **R foot with wound dressing**
- Neurological: sensation intact to light touch
- Skin: warm, dry
- Psychiatric: not agitated, alert and oriented x 3

NECK MASS



Excisional biopsy of a left neck nodule for diagnosis was done and pending results

SYMPTOMS

Renal
Polyuria
Polydipsia
Nephrolithiasis
Nephrocalcinosis
Distal renal tubular acidosis
Nephrogenic diabetes insipidus
Acute and chronic renal insufficiency
Gastrointestinal
Anorexia, nausea, vomiting
Bowel hypomotility and constipation
Pancreatitis
Peptic ulcer disease

Musculoskeletal
Muscle weakness
Bone pain
Osteopenia/osteoporosis
Neurologic
Decreased concentration
Confusion
Fatigue
Stupor, coma
Cardiovascular
Shortening of the QT interval
Bradycardia
Hypertension

ADMISSION LABS

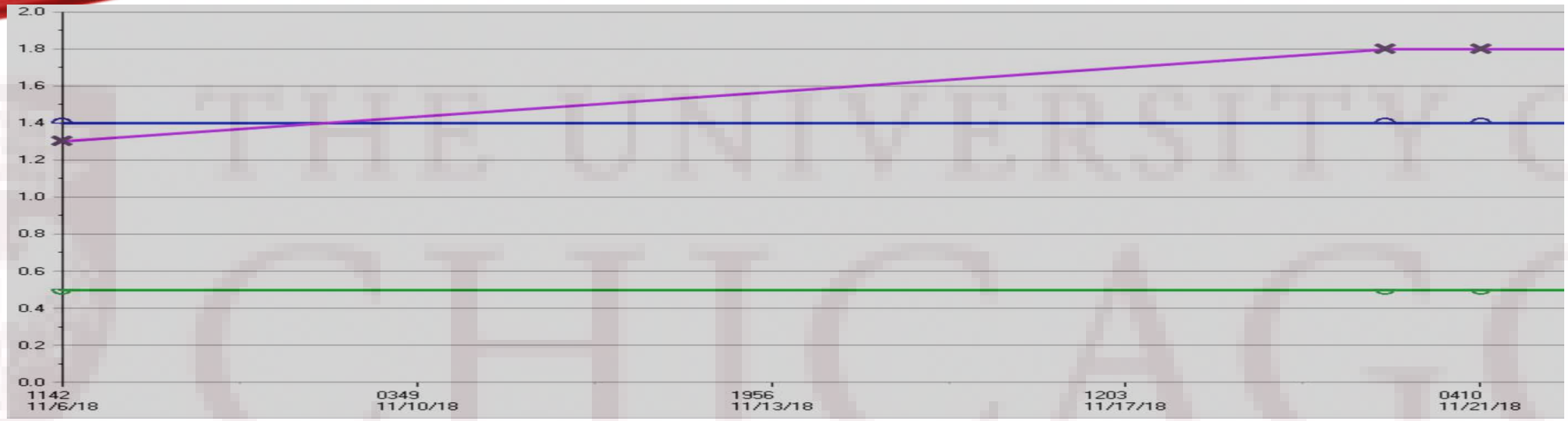
WBC	9.1
RBC	4.45
Hemoglobin	9.9
Hematocrit	31.6
MCV	71.0
MCH	22.2
MCHC	31.3
RBC Dist Width	20.3
Platelet Count	178
Mean Platelet Volume	9.2

Glucose, Ser/Plasma	73 *
Sodium	132
Potassium, Ser/Plasma	4.4
Chloride	94
Carbon Dioxide	28
Anion Gap	10
BUN	36
Creatinine	1.8
GFR Estimate (Calc)	38 *
Calcium	14.8 *
Inorganic Phosphate	2.8
Magnesium	2.6

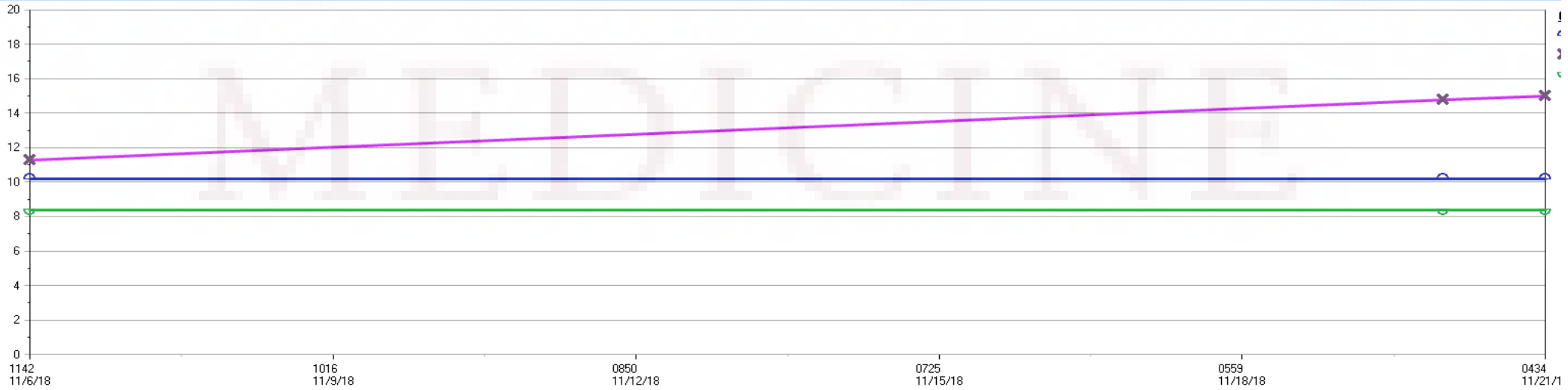
Albumin 2.9

CA AND CR

Cr



Calcium



ADMISSION LABS

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Albumin 2.9

Actual Ca++	4.90	7.58 *	
PTH, Intact		12	

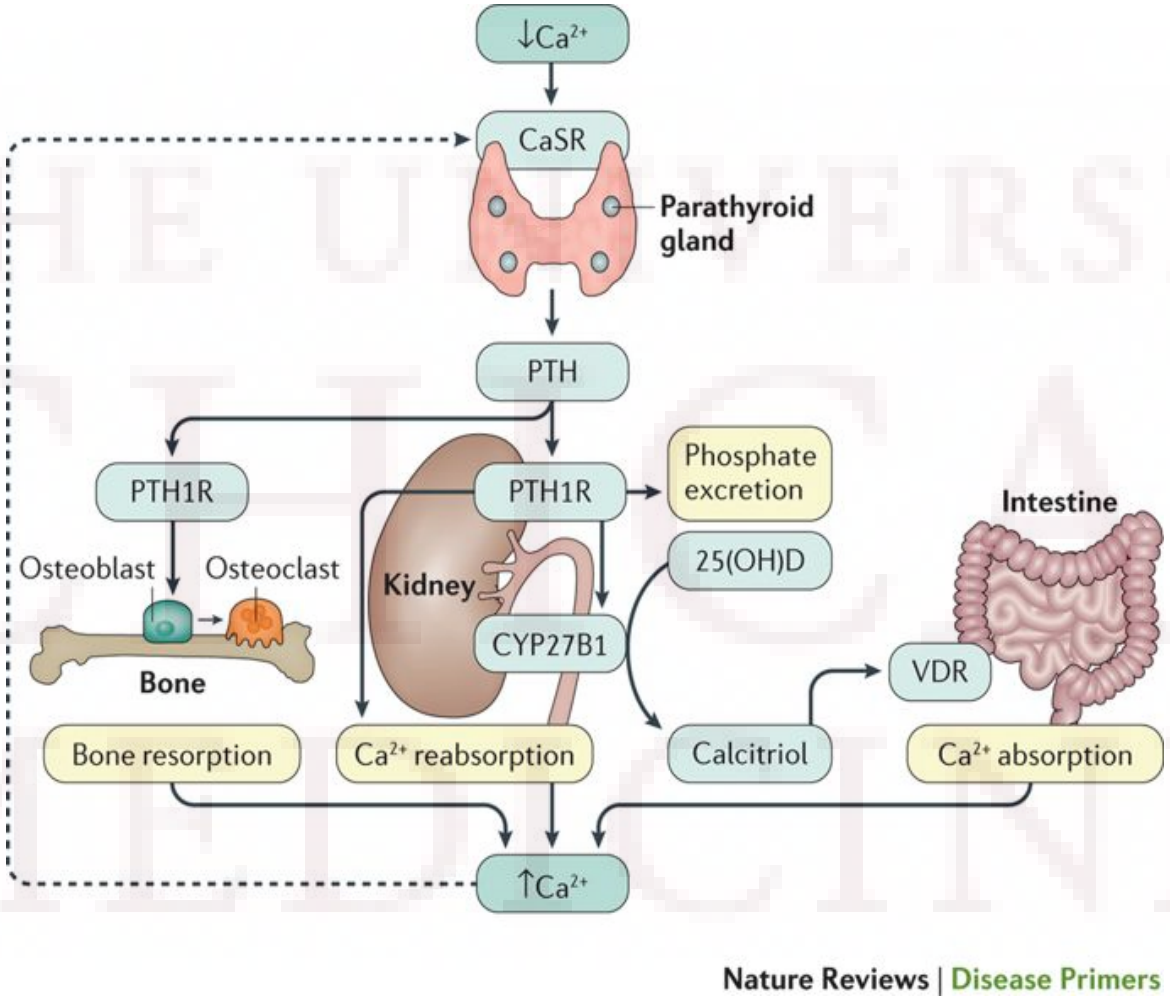
1,25 OH Vit. D: <8

TUMOR MARKER PTH R...		10 !	
25-Hydroxy Vitamin D			<12 *

THYROID FUNCTION	
Thyroxine, Free	1.07
Thyrotropin	7.23
Triiodothyronine	79

Other labs?

HYPERCALCEMIA



Can you list some of the differential diagnosis for Hypercalcemia?

Michael et al., nature 2017

HYPERCALCEMIA DDX

Causes of hypercalcemia

Parathyroid mediated
Primary hyperparathyroidism (sporadic)
Inherited variants
Multiple endocrine neoplasia (MEN) syndromes
Familial isolated hyperparathyroidism
Hyperparathyroidism-jaw tumor syndrome
Familial hypocalciuric hypercalcemia
Tertiary hyperparathyroidism (renal failure)

Non-parathyroid mediated
Hypercalcemia of malignancy
PTHrp
Increased calcitriol (activation of extrarenal 1 alpha-hydroxylase)
Osteolytic bone metastases and local cytokines
Vitamin D intoxication
Chronic granulomatous disorders
Increased calcitriol (activation of extrarenal 1-alpha-hydroxylase)

Medications
Thiazide diuretics
Lithium
Teriparatide
Abaloparatide
Excessive vitamin A
Theophylline toxicity

Miscellaneous
Hyperthyroidism
Acromegaly
Pheochromocytoma
Adrenal insufficiency
Immobilization
Parenteral nutrition
Milk-alkali syndrome

CANCER INDUCED HYPERCALCEMIA

- Common in stage IV cancer and associated with poor prognosis
- Retrospective analysis of nearly 8,000 hypercalcemia of malignancy patients (serum calcium >12 mg/dL), found a 12-month survival rate of only 25%
- In the US and Europe, primary tumors of the lung and breast, and multiple myeloma are the most common hypercalcemia-associated malignancies, followed by squamous-cell carcinoma of the head and neck (SCCHN), renal, and ovarian cancer

Mechanisms?

MECHANISMS

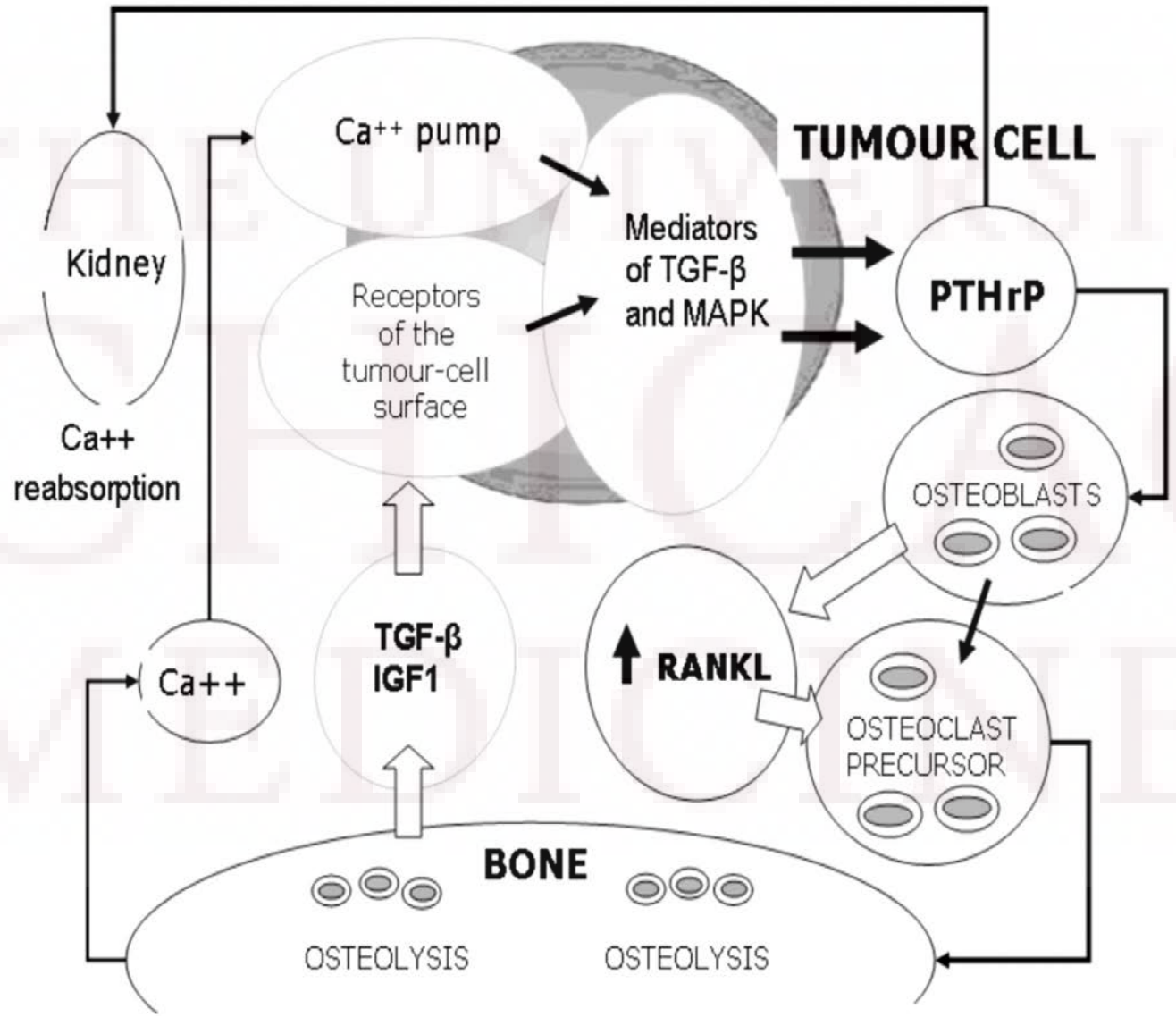
- Coexistence of hyperparathyroidism (5-10% of patients with concomitant cancer-related hypercalcemia,
➔high PTH

Table 1. Types of Hypercalcemia Associated with Cancer.*

Type	Frequency (%)	Bone Metastases	Causal Agent	Typical Tumors
Local osteolytic hypercalcemia	20	Common, extensive	Cytokines, chemokines, PTHrP	Breast cancer, multiple myeloma, lymphoma
Humoral hypercalcemia of malignancy	80	Minimal or absent	PTHrP	Squamous-cell cancer, (e.g., of head and neck, esophagus, cervix, or lung), renal cancer, ovarian cancer, endometrial cancer, HTLV-associated lymphoma, breast cancer
$1,25(OH)_2D$-secreting lymphomas	<1	Variable	$1,25(OH)_2D$	Lymphoma (all types)
Ectopic hyperparathyroidism	<1	Variable	PTH	Variable

Stewart AF. Clinical practice. Hypercalcemia associated with cancer. N Engl J Med. 2005 Jan

PTH-RP



Lumachi F, Brunello A, Roma A, Basso U. Cancer-induced hypercalcemia. Anticancer Res. 2009

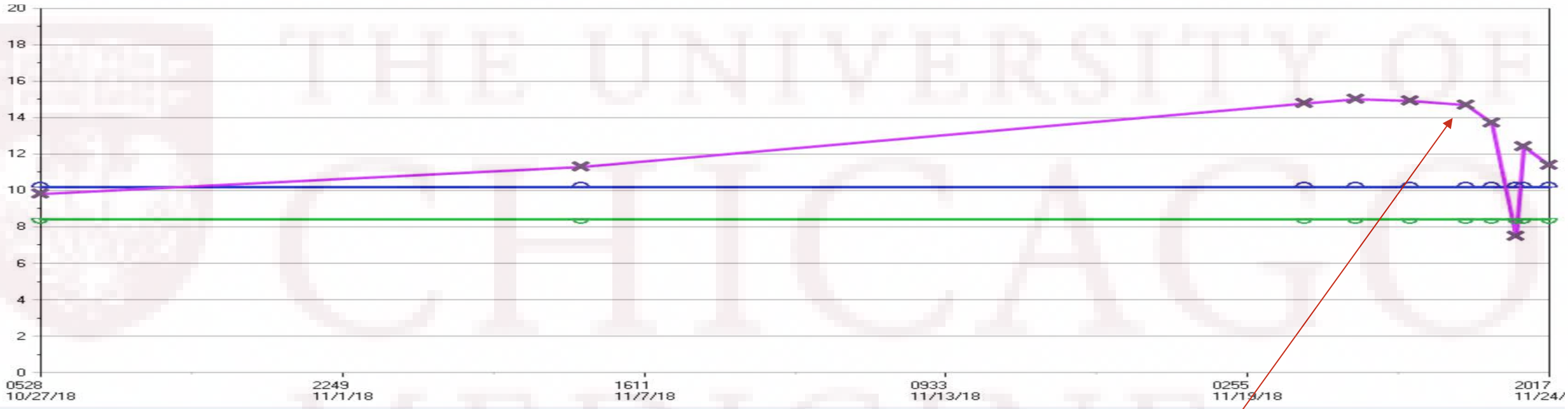
HOW WOULD YOU TREAT THIS PATIENT ?

MANAGEMENT

Treatment of hypercalcemia

Intervention	Mode of action	Onset of action	Duration
Isotonic saline hydration	Restoration of intravascular volume Increases urinary calcium excretion	Hours	During infusion
Calcitonin	Inhibits bone resorption via interference with osteoclast function Promotes urinary calcium excretion	4 to 6 hours	48 hours
Bisphosphonates	Inhibit bone resorption via interference with osteoclast recruitment and function	24 to 72 hours	2 to 4 weeks
Loop diuretics*	Increase urinary calcium excretion via inhibition of calcium reabsorption in the loop of Henle	Hours	During therapy
Glucocorticoids	Decrease intestinal calcium absorption Decrease 1,25-dihydroxyvitamin D production by activated mononuclear cells in patients with granulomatous diseases or lymphoma	2 to 5 days	Days to weeks
Denosumab	Inhibits bone resorption via inhibition of RANKL	4 to 10 days	4 to 15 weeks
Calcimimetics	Calcium-sensing receptor agonist, reduces PTH (parathyroid carcinoma, secondary hyperparathyroidism in CKD)	2 to 3 days	During therapy
Dialysis	Low or no calcium dialysate	Hours	During treatment

BACK TO THE PATIENT



Zometa 3 mg once
Calcitonin 200 IU (x2)

CALCITONIN

- Works by:
  - Increases renal calcium excretion
  - Decrease bone resorption via interference with osteoclast function
- Given as (IU/kg) IM or SubQ. q 12 hours; (doses 6 to 8 IU/kg)
- It works rapidly (within 4-6 hours), but lower Ca only by 1 - 2 mg/dL
- The efficacy of calcitonin is limited to the first 48 hours, even with repeated doses. This might be due to the development of tachyphylaxis, perhaps due to receptor downregulation

CALCITONIN

- Calcitonin can beneficial in symptomatic patients with calcium >14 mg/L, when combined with hydration and bisphosphonates
- Calcitonin and hydration provide a rapid reduction in serum calcium concentration, while a bisphosphonate provides a more sustained effect

Case report

Calcitonin might be useful for hypercalcemia of malignancy resistant to bisphosphonates
(A 73-year-old woman developed hypercalcemia of malignancy while taking weekly alendronate. The patients' serum calcium remained above 15 mg/dL despite hydration and loop diuretics for 48 hours in addition to the bisphosphonates, and resistance was suspected. Intravenous calcitonin produced a dramatic decrease within 12 hours)

Diskin et al.,2007

BISPHOSPHONATES

- Works by inhibiting calcium release by interfering with osteoclast-mediated bone resorption
- FDA approved 2 medications of choice in the treatment of mild-to-severe hypercalcemia associated with cancer:
  - Pamidronate
  - Zoledronate
- Bisphosphonates are nephrotoxicity, specifically pamidronate-induced collapsing focal segmental glomerulosclerosis and acute tubular necrosis (ATN) with zoledronate

Used in patients with kidney injury?

- Hypercalcemia ➔renal dysfunction and effective treatment of hypercalcemia ➔improves renal function (with hydration)

ZOLEDRONATE

- Zoledronate is one thousand times more potent than pamidronate
- Typically dose at 4 mg injection
- It is superior to pamidronate in the rate of normocalcemia, duration of control of CIH and time to relapse

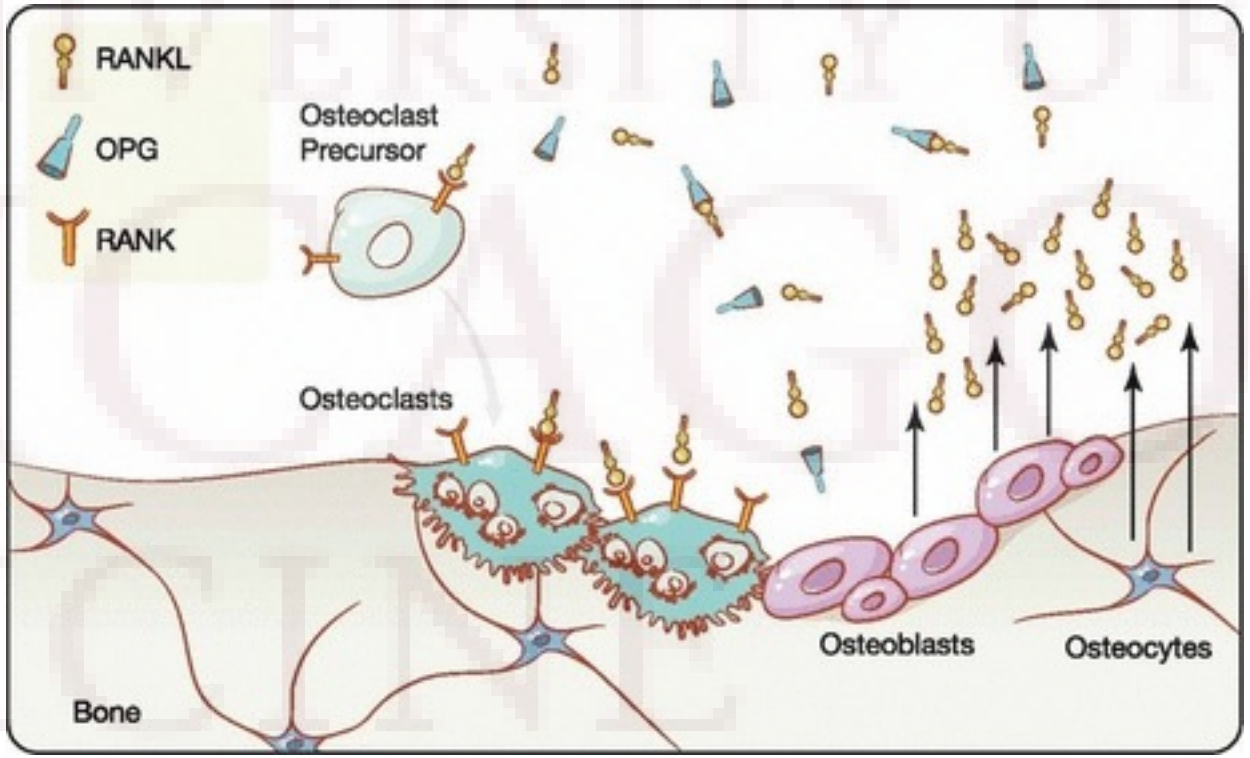
ZOLEDRONATE

- **RCT:** (Major et al, j clin oncol 2001) total of 275 pts were evaluated for efficacy. Both doses (4 or 8 mg)of zoledronic acid were superior to pamidronate in the treatment of CIH
- **Complete response** rates by day 10 were 88.4% (*P* = .002), 86.7% (*P* = .015), and 69.7% for zoledronic acid 4 mg and 8 mg and pamidronate 90 mg, respectively
- **Normalization o**f CSC occurred by day 4 in approximately 50% of patients treated with zoledronic acid and in only 33.3% of the pamidronate-treated patients
- **Median duration of complete response** favored zoledronic acid 4 and 8 mg over pamidronate 90 mg with response durations of 32, 43, and 18 days, respectively

Major et al, j clin oncol 2001

DENOSUMAB

- A fully human monoclonal antibody, binds RANKL to inhibit the formation, function, and survival of osteoclasts



Int J Clin Pract. 2012 Dec;

Denosumab for Treatment of Hypercalcemia of Malignancy

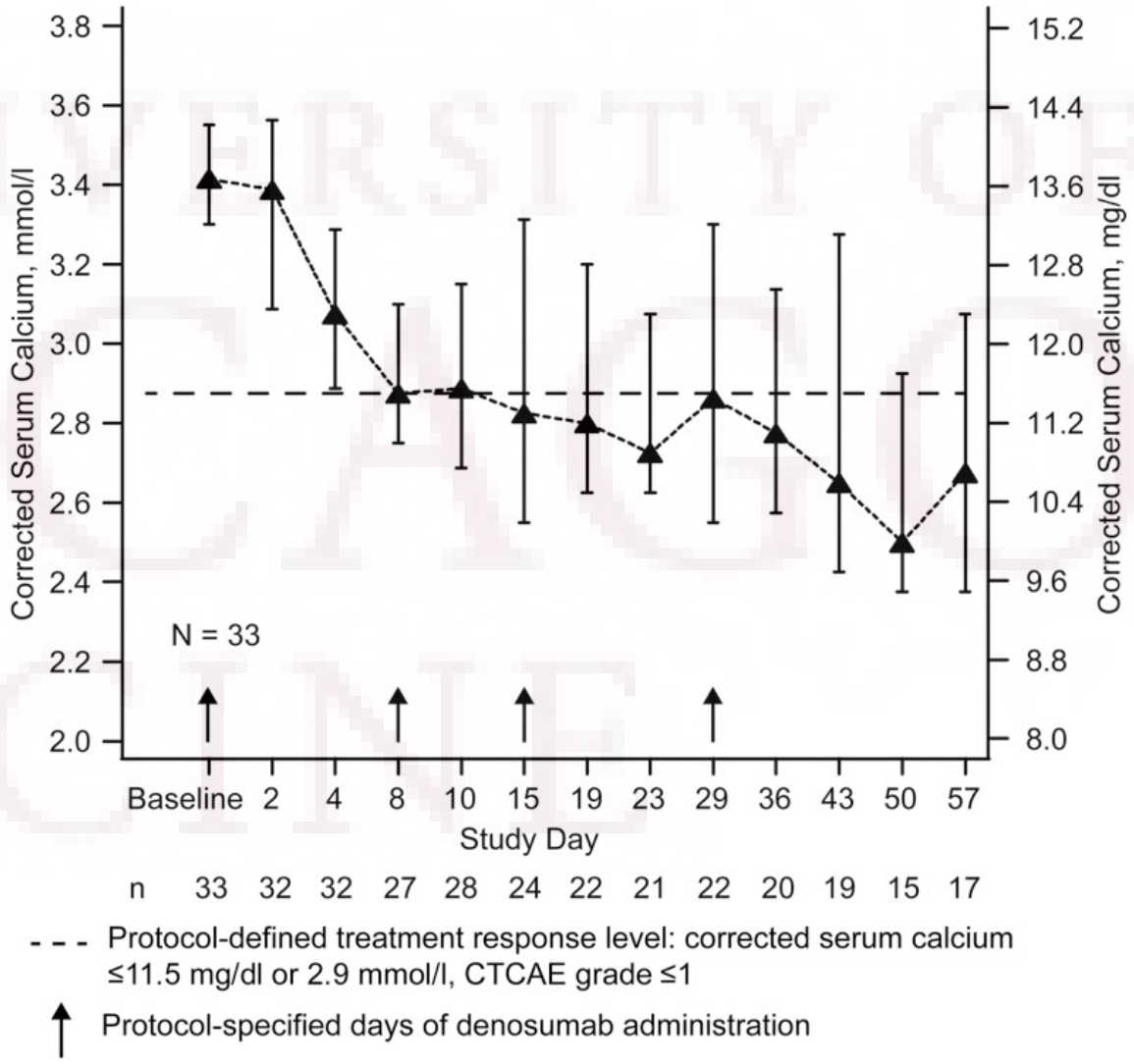
Mimi I. Hu, Ilya G. Glezerman, Sophie Leboulleux, Karl Insogna, Rasim Gucalp, Waldemar Misiorowski, Bennett Yu, Paul Zorsky, Diego Tosi, Alberto Bessudo, Arnaud Jaccard, Giuseppe Tonini, Wendy Ying, Ada Braun, and Rajul K. Jain

- Single-arm international study
- Participants had serum calcium levels corrected for albumin (CSC) >12.5 mg/dL (3.1 mmol/L) despite bisphosphonates given >7 and ≤30 days before screening
- Evaluated denosumab (120 mg) for treatment of CIH

J Clin Endocrinol Metab. 2014 Sep

PHASE 2 STUDY

Primary tumor type (%)	
Solid tumors	24 (73)
Breast	6 (18)
Neuroendocrine	4 (12)
Non-small-cell lung cancer	3 (9)
Renal cell	3 (9)
Head and neck	2 (6)
Adenocarcinoma with unknown primary site	1 (3)
Bladder	1 (3)
Liver	1 (3)
Ovarian	1 (3)
Small-cell lung cancer	1 (3)
Soft tissue sarcoma	1 (3)
Hematologic malignancies	9 (27)
Myeloma	5 (15)
Chronic lymphocytic leukemia with Richter's transformation	2 (6)
Non-Hodgkin lymphoma	2 (6)
Metastatic disease at baseline, n (%)	30 (91)
Presence of bone metastasis at baseline, n (%)	13 (39)
Months from initial cancer diagnosis to enrollment, median (Q1, Q3)	30 (10, 84)
Months of prior bisphosphonate use, median (range)	4 (1–41)
Number of doses of intravenous bisphosphonates, median (range)	5 (1–42)
Days from last intravenous bisphosphonate treatment to enrollment, median (Q1, Q3)	17 (13, 22)
Patients reporting symptoms attributed to hypercalcemia at baseline, n (%)[a]	19 (58)
Fatigue	9 (27)
Anorexia	5 (15)
Nausea	4 (12)
Constipation	4 (12)
Lethargy	4 (12)
Other[b]	22 (56)
Calcium level (albumin corrected), median (range), mg/dL[c,d]	13.7 (11.9–17.3)
PTHrP level, median (range), pmol/L[e]	4.2 (0.5–24.0)



J Clin Endocrinol Metab. 2014 Sep;

Denosumab Efficacy in HCM[a]

	Patients Experiencing a Treatment Response (CSC ≤11.5 mg/dL)		Patients Experiencing a Complete Response (CSC ≤10.8 mg/dL)	
	By Day 10	**Over the Course of the Study**	**By Day 10**	**Over the Course of the Study**
Overall population, N = 33	21 (64)	23 (70)	12 (36)	21 (64)
Patient subgroups (characteristics at baseline)				
Gender				
Women, n = 12	5 (42)	7 (58)	4 (33)	6 (50)
Men, n = 21	16 (76)	16 (76)	8 (38)	15 (71)
Age				
<65 y, n = 19	12 (63)	12 (63)	6 (32)	11 (58)
≥65 y, n = 14	9 (64)	11 (79)	6 (43)	10 (71)
Racial group				
Caucasian, n = 23	14 (61)	15 (65)	9 (39)	14 (61)
Non-Caucasian, n = 10	7 (70)	8 (80)	3 (30)	7 (70)
Bone metastases				
Bone metastases, n = 13	7 (54)	8 (62)	3 (23)	6 (46)
No bone metastases, n = 20	14 (70)	15 (75)	9 (45)	15 (75)

J Clin Endocrinol Metab. 2014 Sep;

Denosumab in hypercalcemia of malignancy: A case series

Amanda Dietzek[1], Kelly Connelly[2], Michael Cotugno[3], Sylvia Bartel[1,3] and Anne M McDonnell[3]

- A total of 7 patients, who received denosumab for CIH
- No PTHrP levels
- All patients in this study received multiple prior therapies for CIH
- 5 /7 patients who received bisphophonate for CIH, achieved normalized corrected Ca levels within 17h after denosumab administration
- One patient developed hypocalcemia (Ca 6.6mg/dL), which manifested 86h after denosumab (60mg) was administered

Age median (range)	64 (52–81)
Gender	
Male	2
Female	5
Malignancy	
Breast	3
CUP	1
Multiple myeloma	1
Non-Hodgkin lymphoma	1
Sarcoma	1
Visceral metastases	
Yes	3
No	4
Prior therapy	
Chemotherapy	6
Recent chemotherapy	4
Hormonal therapy	2
Densosumab dose	
120 mg	5
60 mg	2
Previous hypercalcemia therapies	
Bisphosphonate	6
Cortcocosteroids	3
Icitonin	5
Hydration	7
Days from admission to denosumab administration mean (SD)	6.3 (4.6)

CUP: cancer of unknown primary.

J Oncol Pharm Pract. 2015 Apr;21(2):143-7. Epub 2014 Jan 10.

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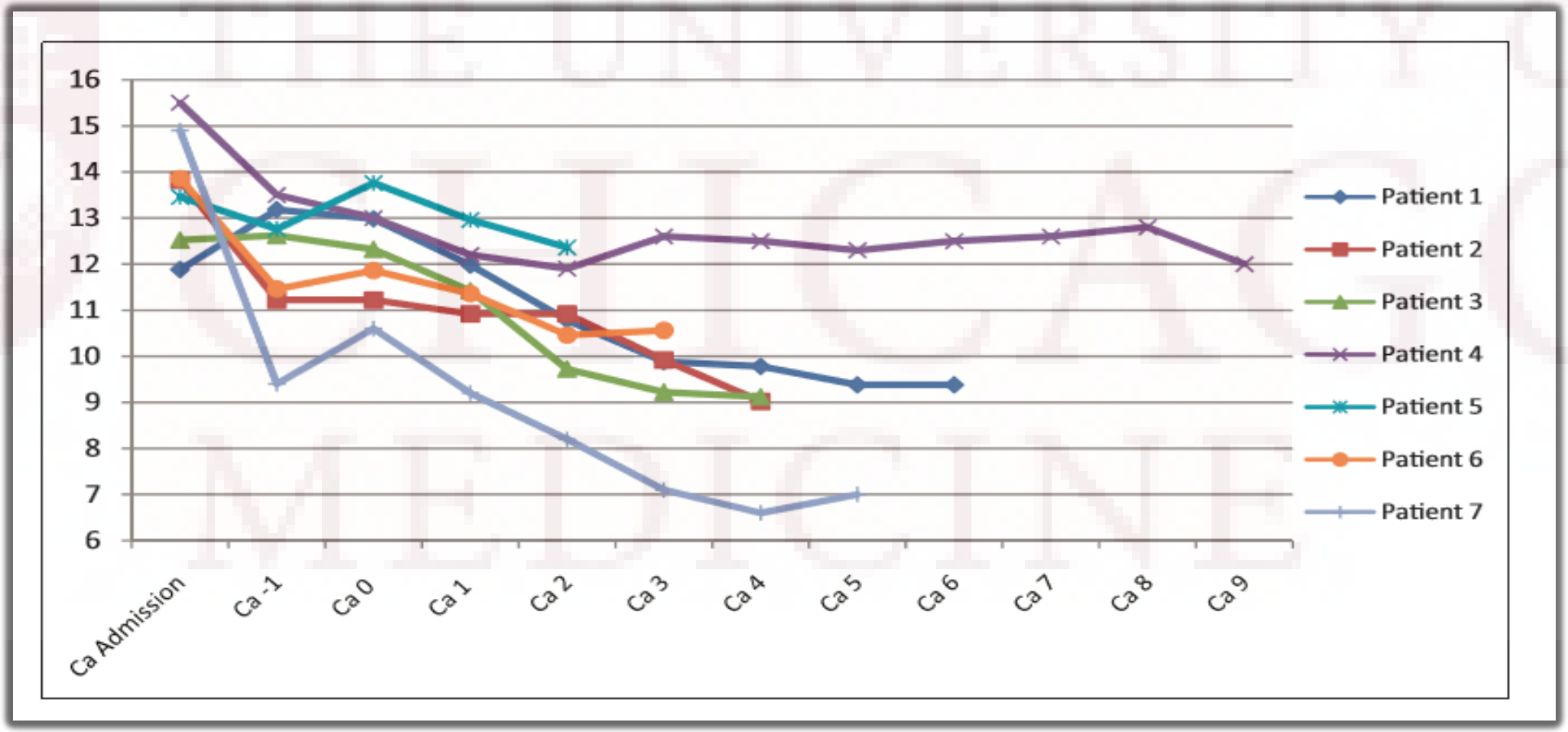

J Oncol Pharm Pract. 2015 Apr;21(2):143-7. Epub 2014 Jan 10.

BACK TO THE PATIENT

- His Ca was normalized after Zometa and IV fluids
- He was discharged home after few days
- Was readmitted due to AFIB with RVR and his Ca continued to be normal
- Palliative consult recommended comfort care due to functional status decline
- He accepted hospice

OBJECTIVES

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REFERENCES

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THANK YOU

Questions/comments?