

69 year old woman with hypercalcemia

Katie Stanley, MD

March 6, 2014

HPI

- 69 yo F with CLL and SCC of bladder
- Presented with abdominal pain, decreased PO intake, fatigue, generalized weakness, constipation, pelvic pain
- Symptoms worsening x 1-2 weeks
- Neither she nor husband note mental status changes
- Found to have Ca of 11.8 (corrected 12.4)
- No prior hypercalcemia
- On MVI, no other Ca or vit D

Oncologic history

- Presented 9/2013 with difficulty urinating, dysuria, vaginal spotting, wt loss, bloody diarrhea
- CT showed extensive retroperitoneal LAD and splenomegaly, severe bilateral hydronephrosis with level of obstruction at bladder
- CBC showed 62% lymphocytes with some cells suspicious for malignant lymphoid cells

Oncologic history

- Inguinal LN bx and BM cx c/w small lymphocytic lymphoma/CLL
- Cystoscopy-> 4 cm bladder mass resected c/w squamous cell carcinoma of bladder
- Bilateral nephrostomy tubes placed
- Has received 3 cycles of bendamustine/rituximab with subsequent decrease in LAD
- Seeking coverage for ibrutinib to further decrease LAD prior to cystectomy, pelvic LN dissection, ileal conduit

Other History

- Other PMH
 - HTN
 - DM2
 - H/o GI bleed x 2
- Family History
 - No calcium disorders
- Social History
 - Married
 - Used to work as nurse's aid
 - Former smoker ½ ppd x 4 yrs, quit 2010
- Home Medications
 - Acyclovir
 - Amlodipine
 - ASA
 - Dapsone
 - Nexium
 - MVI
 - Metoprolol
 - Lantus and Novolog
 - Metformin
 - Remeron
 - Miralax
 - Peri-Colace
 - Tramadol prn

Review of Systems

- Constitutional: Positive for appetite change, fatigue and unexpected weight change. Negative for fever.
- Respiratory: Negative for shortness of breath.
- Cardiovascular: Positive for chest pain. Negative for leg swelling.
- Gastrointestinal: Positive for abdominal pain, constipation and abdominal distention. Negative for nausea and vomiting.
- Genitourinary: Positive for pelvic pain. Negative for decreased urine volume.
 - B/I nephrostomy tubes
- Musculoskeletal: Negative for joint swelling.
- Skin: Negative for rash.
- Neurological: Positive for weakness. Negative for dizziness and light-headedness.
- Hematological: CLL
- Psychiatric/Behavioral: Negative for confusion and decreased concentration.

Physical Exam

- Wt 42 kg, Ht 162.6 cm, BMI 15.9, T36.8, HR 70, RR 16, BP 116/39, SaO2 98% RA
- Constitutional: No distress. Cachectic appearing
- Head: Normocephalic and atraumatic. Tachy MM
- Eyes: Conjunctivae normal are normal.
- Neck: Neck supple. No thyromegaly present.
- Cardiovascular: Normal rate, regular rhythm, normal heart sounds and intact distal pulses.
- Pulmonary/Chest: Effort normal and breath sounds normal.
- Abdominal: Soft. She exhibits distension. There is no tenderness.
- Musculoskeletal: She exhibits no edema.
- Neurological: She is alert. She has normal reflexes. Poor historian but answered questions appropriately
- Skin: Skin is warm and dry. She is not diaphoretic. Cap refill < 2sec
- Psychiatric: She has a normal mood and affect.

Initial Labs

- Na 122 K 5.8 Cl 85 HCO₃ 29 BUN 26 Cr 1.1 Ca 11.8
- Prot 7.2 Alb 2.7 Bili 0.5 Alk phos 121 AST 23 ALT 8
- WBC 10.3 Hgb 10.6 Plts 345
- PTH 22 with Ca 11.4 Mg 2.1 PO₄ 3.5

Differential Diagnosis

- PTH-mediated
 - Primary hyperparathyroidism
 - Tertiary hyperparathyroidism
 - **PTHrp mediated**
- Non PTH mediated
 - **1,25OH-vitamin mediated**
 - CLL
 - Granulomatous disease
 - Milk alkali syndrome
 - Vitamin D intoxication
 - Hyperthyroidism
 - Adrenal insufficiency
 - Renal insufficiency
 - **Osteolytic metastases**

Further workup and initial management

- IVF at 150 ml/hr
- TSH 3.65 FT4 1.18
- Cortisol 17.3 ACTH 19.5
- 25OH-D, 1,25OH-D, PTHrp pending
- Bisphosphonate or steroids?
 - Start with bisphosphonate, but...
 - Make sure not vitamin D deficient first

Course

Date	2/10	2/11	2/12	2/13
Calcium	11.8	11.4	11.5	11.6
Cr	1.1	1.0	0.9	0.7
BUN	26	26	23	17
GFR	49	55	62	83

25OH-D 36

Pamidronate 60 mg IV x 1 given 2/13 pm

1,25OH-vitamin D 38

Course

Date	2/14	2/15	2/16	2/17	2/18
Calcium	12.4	13.0	12.2	11.6	11.4 (12.4)
Cr	0.7	0.8	1.1	1.2	1.3
BUN	14	15	22	28	33
GFR	83	71	49	45	41

2/15 Fluid overload->stopped IVF, started Lasix

2/15 Started calcitonin 4 mcg/kg q12h

2/17 CT showing progression of disease with peritoneal carcinomatosis

Increased calcitonin to 8 mcg/kg q12h

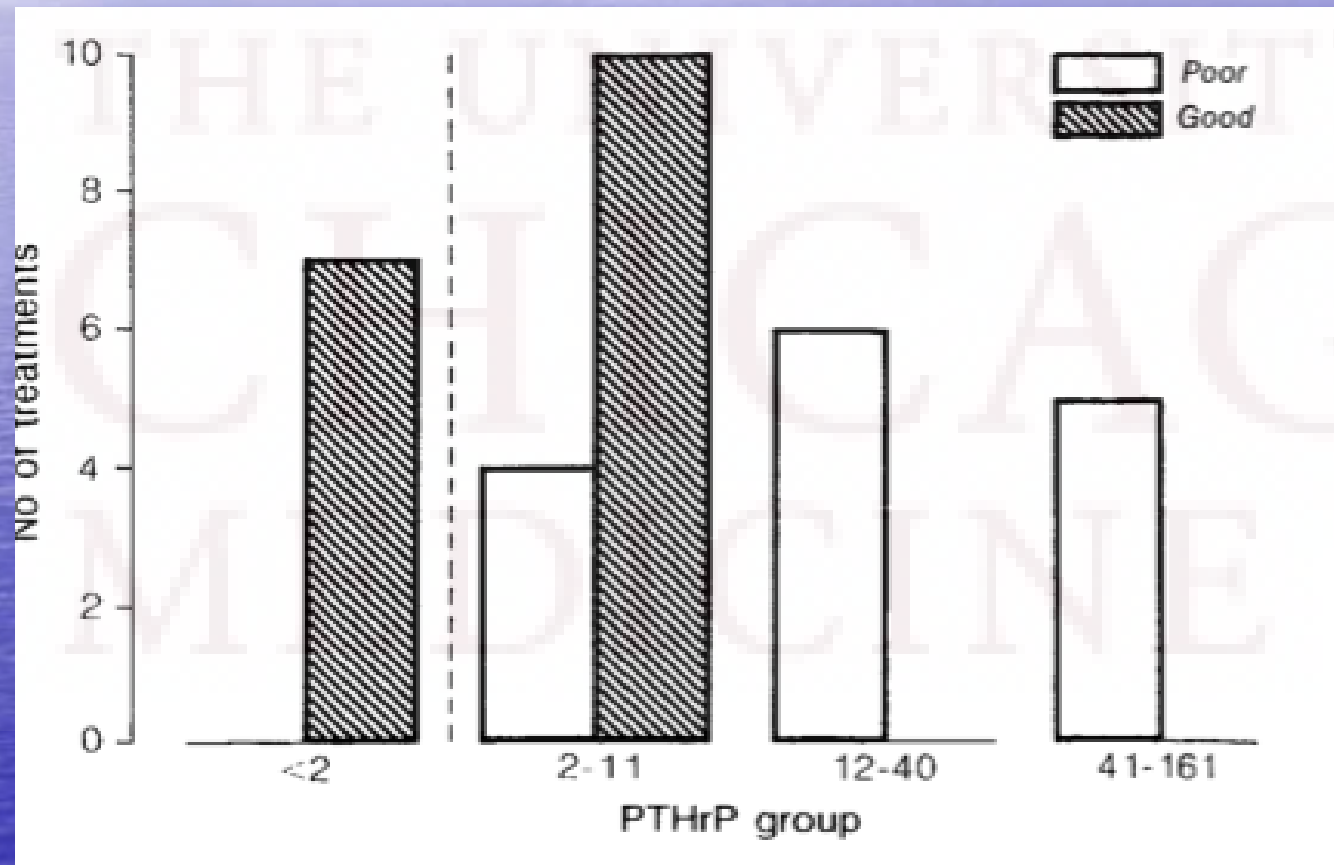
Course

- 2/18 Recommended denosumab 120 mg x 1
 - Not given because not on formulary
- 2/19 am Found unresponsive
 - Intubated and transferred to MICU
- 2/20 Made comfort care and extubated
- PTHrp 5.9 (<2.0)
- 2/21 Pt expired

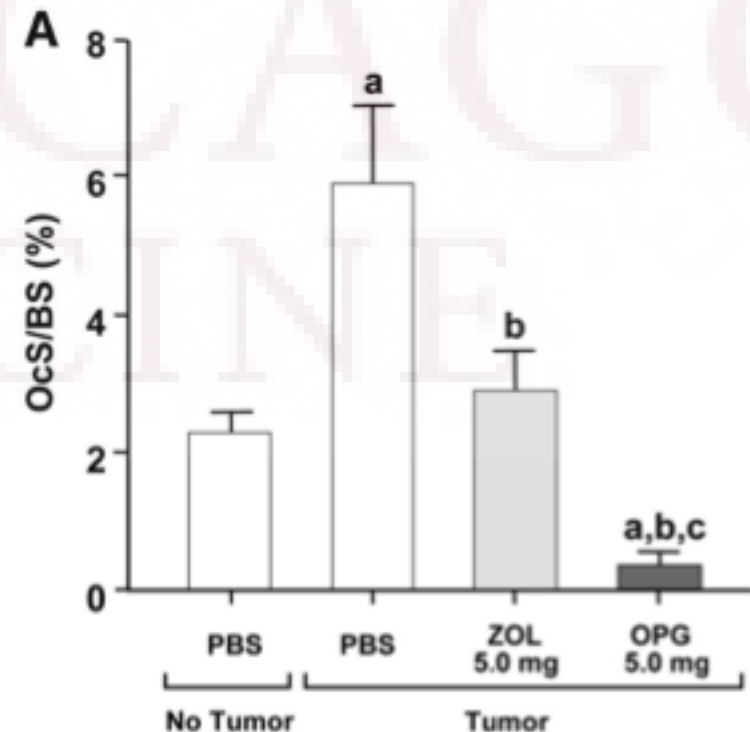
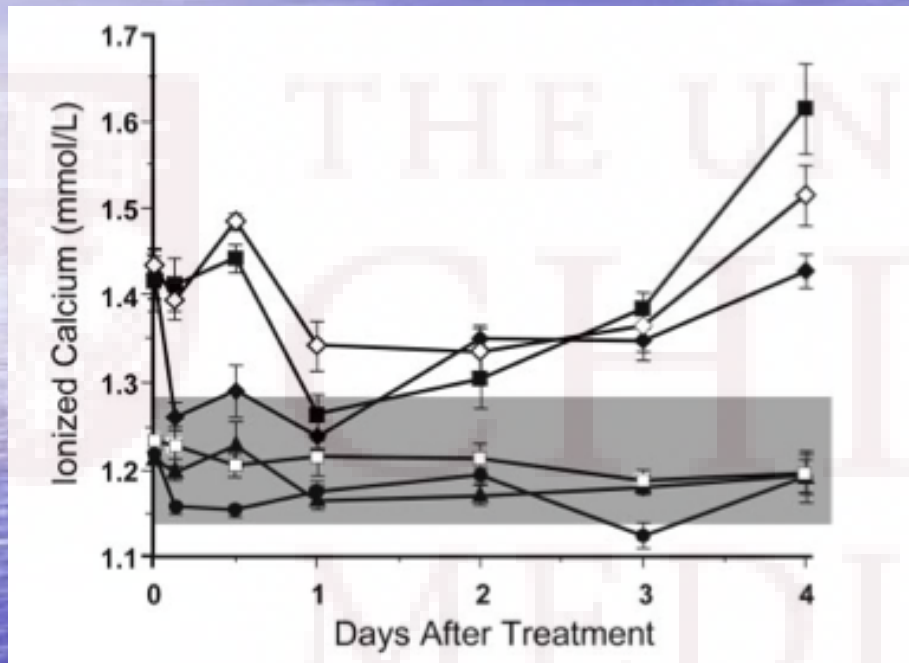
Does level of PTHrp determine response to pamidronate?

- Prospective study of 44 patients with malignant disease and hypercalcemia
- Measured PTHrP, nephogenous cAMP, TmCa, TmP, phosphate
- All treated with 2-3 L NaCl followed by pamidronate
- Defined good response as nl Ca for 14 days or more, poor response as elevated Ca within 14 days

Does level of PTHrp determine response to pamidronate?

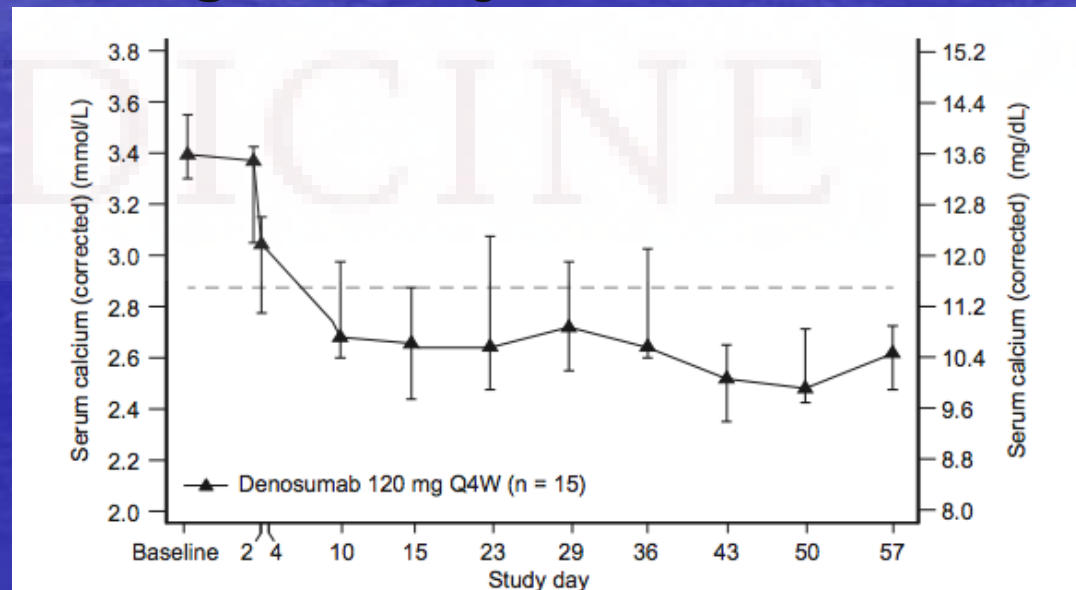


Is there a better treatment for PTHrp-mediated hypercalcemia?



What about using denosumab?

- Open label single arm study of patients with malignancy and $\text{Ca} > 12.5$ 7-30 days after receiving bisphosphonate
- Denosumab 120 mg on days 1, 8, 15, 29 then q4wks



References

- GA Clinies. Mechanisms and treatment of hypercalcemia of malignancy. *Curr Opin Endocrinol Diabetes Obes.* 2011:339-46.
- H Gurney, V Grill, and TJ Martin. Parathyroid hormone-related protein and response to pamidronate in tumour-induced hypercalcaemia. *Lancet.* 1993: 1611-13.
- MI Hu et al. Denosumab for patients with persistent or relapsed hypercalcemia of malignancy despite recent bisphosphonate treatment. *J Natl Cancer Inst.* 2013: 1417-20.
- S Morony et al. The inhibition of RANKL causes greater suppression of bone resorption and hypercalcemia compared with bisphosphonates in two models of humoral hypercalcemia of malignancy. *Endocrinology.* 2005: 3235-43.