63 Year Old Female presented with AMS

Milad Abusag

Fellow section of Endocrinology Diabetes and Metabolism

04/03/2014

HPI

- 63 year old F with PMH of DM type II, Hep C, metastatic NSCLC presented with AMS.
- Was in her usual state of health until 11/2013
- c/o hemoptysis → NSCLC → multiple osseous lesions (ribs, Lt femor, bilateral iliac bones)
- In January/2014 admitted to OSH with AMS and found to have corrected Ca of 21.
- In 2/2014 found to have pathological fracture of Lt femur underwent ORIF
- Now presented with AMS and found to have a Ca of 13.6 (with Albumin 2.6)
- Started on IVF and Endocrine service consulted for further management

PMH:

✓Metastatic NSCLC

✓Hep C

✓DM type II

Family History:

✓Father HTN

✓DM (mother).

Surgical history:

✓Lt femur Fracture s/p ORIF

Social history

✓+ smoking 1.5 PPD for 50 years, h/o alcohol abuse, no illicit drugs.

Home medications

✓**Glipizide XL 10 mg daily**

✓**Ibuprofen 200 mg po Q 8hrs PRN**

✓**Lopressor XL 12.5 mg dailu**

✓**Lisinopril 40 mg po daily**

✓**Miralax PRN**

✓**Oxycodone 5 mg po Q 8hrs PRN**

ROS

Non Obtainable: due to patient general condition

On examination

Vitals: BP 107/78 | Pulse 98, no fever, RR 18. BMI 31

General: confused, not oriented to time, place or person

HEENT: normocephalic non traumatic, + pallor

Neck: supple, no LN enlargement, no thyromegaly

CVS/Pulm: bilateral inspiratory crackles basally, S1 + S2, no murmur.

Abd: soft lax, no organomegaly, no tenderness, audible bowel sounds.

Skin: warm, no rash, dry mucous membrane

Neuro: confused, difficult to assess CN, DTR symmetrically decreased, no abnormal movements or abnormal positions.

General labs

Test	Result (3/6/2013)
WBC	5.2
Hb	9.8
Plt	103
Glucose	189
Na	146
K	3.8
Anion gap	15
BUN/Cr	48/2.6
GFR (Calc)	34
Ca	13.6 (corrected 14.72)
Albumin	2.6
ALT	16
AST	18
ALP	50

TABLE 3
Causes of Hypercalcemia

Parathyroid hormone-related
- Primary hyperparathyroidism*
  - Sporadic, familial, associated with multiple endocrine neoplasia I or II
- Tertiary hyperparathyroidism
  - Associated with chronic renal failure or vitamin D deficiency

Vitamin D-related
- Vitamin D intoxication
  - Usually 25-hydroxyvitamin D_2 in over-the-counter supplements
- Granulomatous disease sarcoidosis, berylliosis, tuberculosis
- Hodgkin's lymphoma

Malignancy
- Humoral hypercalcemia of malignancy* (mediated by PTHrP)
  - Solid tumors, especially lung, head, and neck squamous cancers, renal cell tumors
- Local osteolysis* (mediated by cytokines) multiple myeloma, breast cancer

Medications
- Thiazide diuretics (usually mild)*
- Lithium
- Milk-alkali syndrome (from calcium antacids)
- Vitamin A intoxication (including analogs used to treat acne)

Other endocrine disorders
- Hyperthyroidism
- Adrenal insufficiency
- Acromegaly
- Pheochromocytoma

Genetic disorders
- Familial hypocalciuric hypercalcemia: mutated calcium-sensing receptor

Other
- Immobilization, with high bone turnover (e.g., Paget's disease, bedridden child)
- Recovery phase of rhabdomyolysis

PTHrP = parathyroid hormone-related peptide.

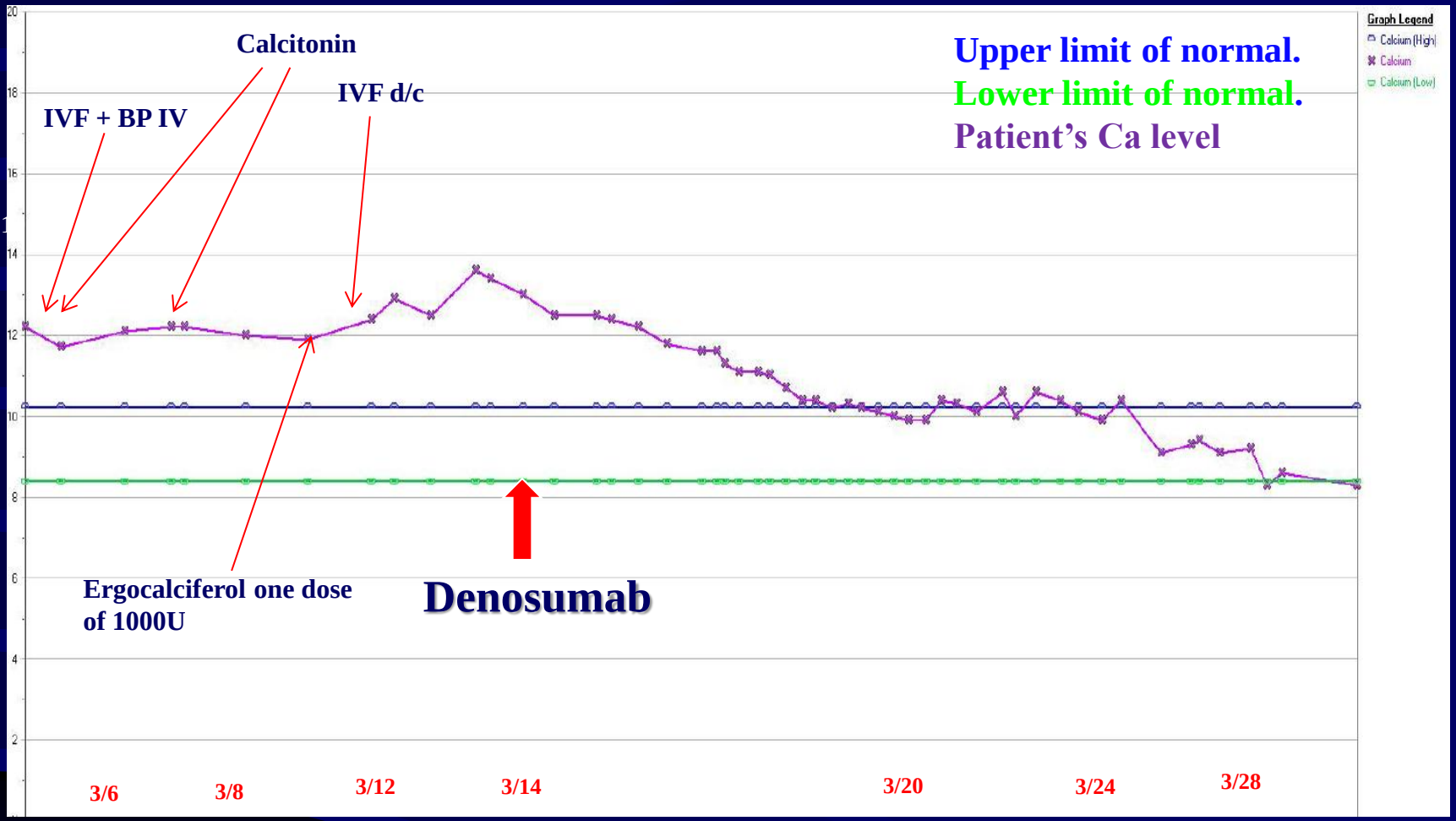
**—The most common causes of hypercalcemia.*

Further workup

Test/date	3/7
25 OH VitD	19
PTH	5

Test/date	3/7
PTH rP	23 (ref <2.0)

Hospital course


Calcitonin
IVF + BP IV
IVF d/c
Upper limit of normal.
Lower limit of normal.
Patient's Ca level
Graph Legend
Calcium (High)
Calcium
Calcium (Low)
Ergocalciferol one dose of 1000U
Denosumab
3/6
3/8
3/12
3/14
3/20
3/24
3/28

Clinical Qs

1. Comparing with bisphosphonate is Denosumab more effective in treatment of hypercalcemia of malignancy ?
2. In patient with bone metastasis is Denosumab more effective in suppression of bone turnover than bisphosphonate?
3. is it ok to replace vitD in pt malignancy associated hypercalcemia and concomitant Vit D deficiency who will receive high potent antiresorptive agents?

Randomized Trial of Denosumab in Patients With Bone Metastases From Prostate Cancer, Breast Cancer, or Other Neoplasms After Intravenous Bisphosphonates

Karim Fizazi, Allan Lipton, Xavier Mariette, Jean-Jacques Body, Yasmin Rahim, Julie R. Gralow, Guozhi Gao, Ling Wu, Winnie Sohn, and Susie Jun

East General Hospital, Toronto, Ontario, Canada.

J Clin Oncol 27:1564-1571.

Endpoint:

- N-telopeptide < 50nmol/L at 13 weeks
- Follow up 25 weeks

109 patients

Inclusion criteria:

1. Histologically confirmed malignancy with one or more bone mets
2. N-telopeptide >50 nmol/L

Denosumab 180mg SQ (n = 74)

IV BP (n = 35)
(zolendronic acid n=30, pamidronate n=5)

Q4 weeks therapy n= 38

Q 12 wks therapy n = 36

completed 25 wks follow up study (n = 53)

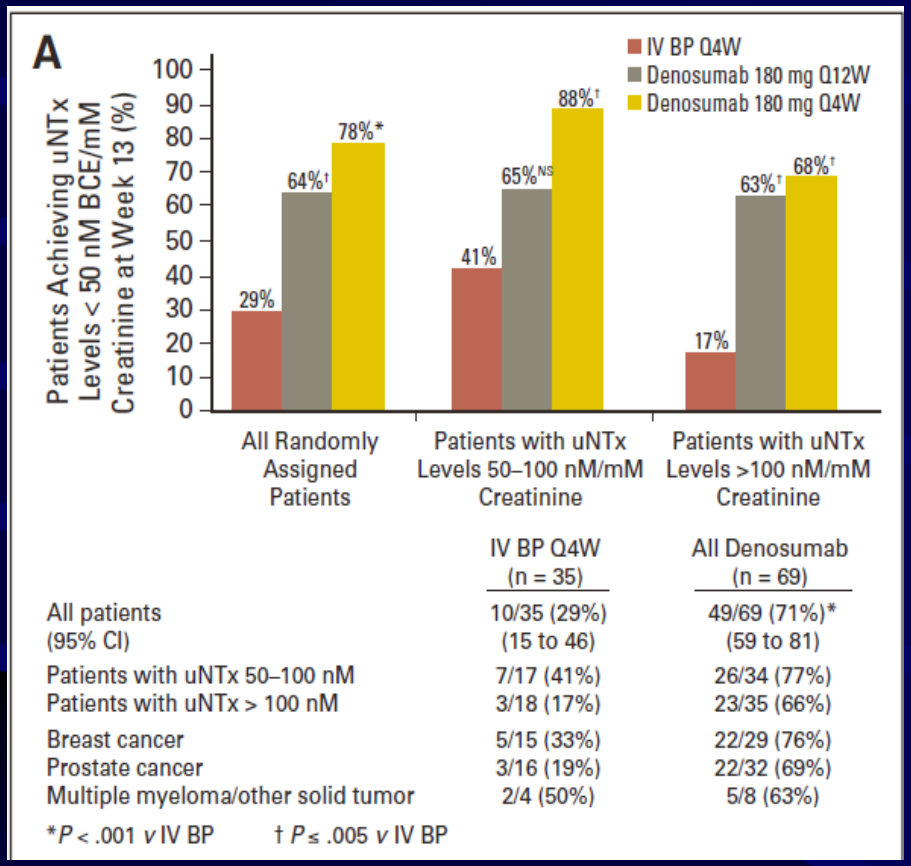
completed 25 wks follow up study (n = 25)

**** All patients received 500 mg Ca and 400-800 U vit D daily supplementation

J Clin Oncol 27:1564-1571. © 2009 by American Society of Clinical Oncology

Effect on bone turnover

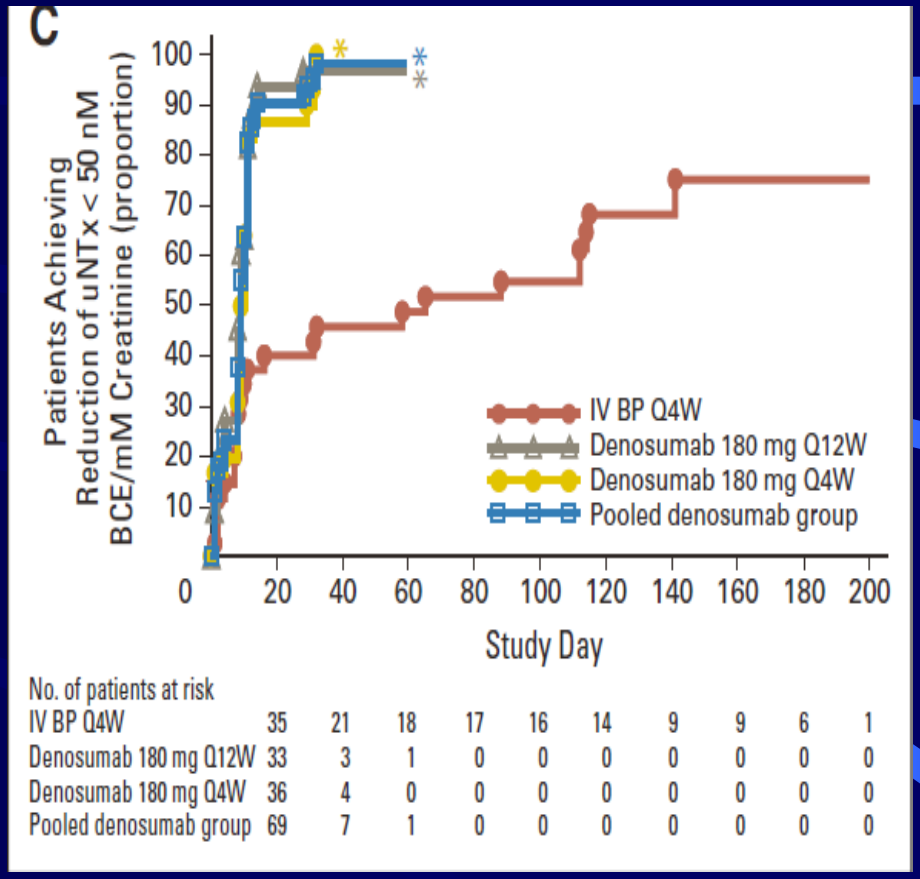
urinary N-telopeptide used as a marker for bone turnover



	IV BP Q4W (n = 35)	All Denosumab (n = 69)
All patients (95% CI)	10/35 (29%) (15 to 46)	49/69 (71%)* (59 to 81)
Patients with uNTx 50–100 nM	7/17 (41%)	26/34 (77%)
Patients with uNTx > 100 nM	3/18 (17%)	23/35 (66%)
Breast cancer	5/15 (33%)	22/29 (76%)
Prostate cancer	3/16 (19%)	22/32 (69%)
Multiple myeloma/other solid tumor	2/4 (50%)	5/8 (63%)

*$P < .001$ *v* IV BP † $P \leq .005$ *v* IV BP

Proportion of patients in each treatment arm achieving urinary N-telopeptide (uNTx) levels lower than 50 nmol/L BCE/mM creatinine at week13.



No. of patients at risk										
IV BP Q4W	35	21	18	17	16	14	9	9	6	1
Denosumab 180 mg Q12W	33	3	1	0	0	0	0	0	0	0
Denosumab 180 mg Q4W	36	4	0	0	0	0	0	0	0	0
Pooled denosumab group	69	7	1	0	0	0	0	0	0	0

Median time to reduction of uNTx levels lower than 50nmol/L BCE/mM creatinine.

J Clin Oncol 27:1564-1571. © 2009 by American Society of Clinical Oncology

Effect on serum Ca level

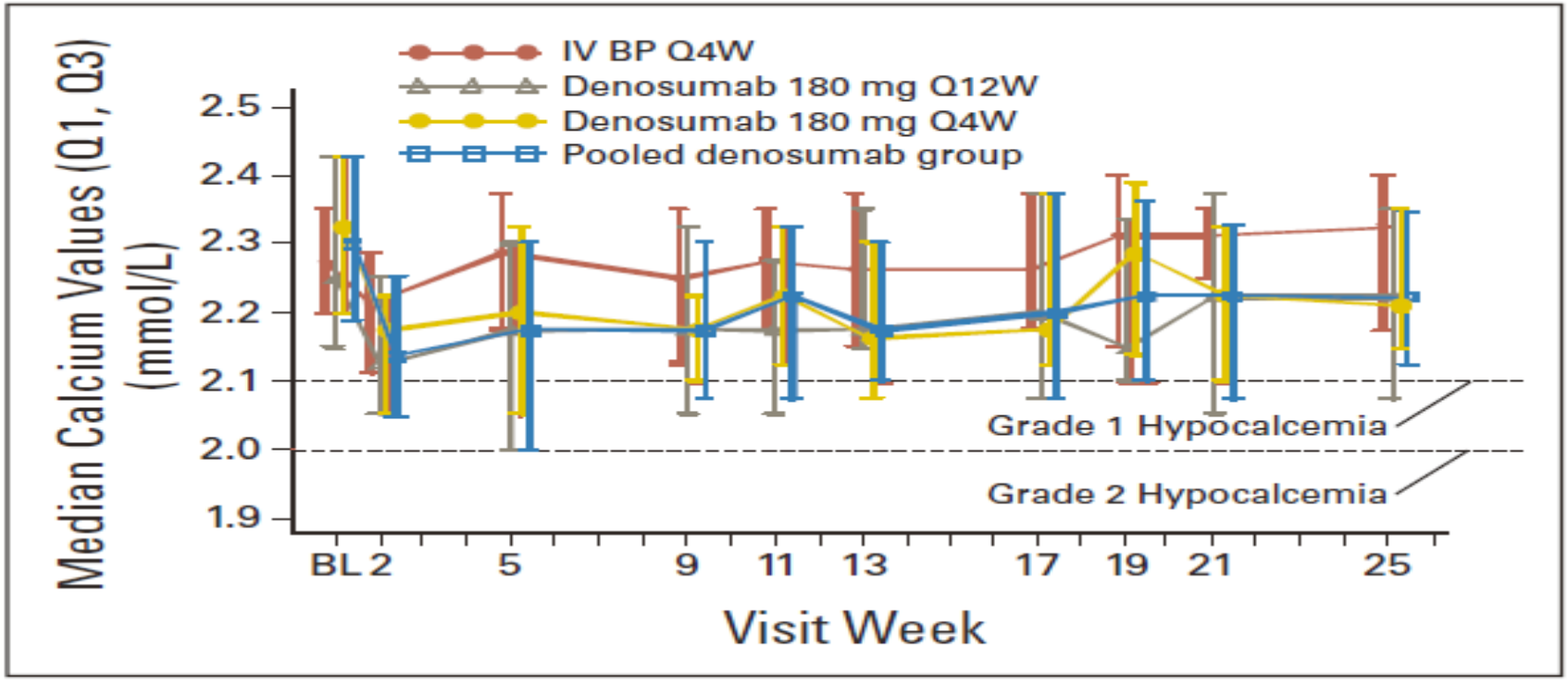


Fig 4. Median albumin-corrected calcium values from baseline to week 25. IV BP, intravenous bisphosphonate; Q4W, every 4 weeks; Q12W, every 12 weeks; BL, baseline.

- **Among denosumab- treated patients, nine (11%) experienced hypocalcemia**
- **Among IV BP–treated patients, one (3%) experienced hypocalcemia.**

Result

- ✓ The primary end point (uNTx 50 at week 13) was achieved by 49 of 69 patients (71%) in the Denosumab arms compared with 10 of 35 patients (29%) in the IV BP arm (*P* .001)
- ✓ The effect of denosumab was rapid and appeared to be consistent regardless tumor types
- ✓ Denosumab was noninferior (trending to superiority) to iv BP to control hypercalcemia of malignancy
- ✓ No neutralizing antidenosumab antibodies and no cases of osteonecrosis of the jaw were reported during the treatment and follow-up periods

Back to my patient

1. Received only one dose of Denusomab 120 mg SQ. Ca normalized
2. Developed acute pancreatitis (lipase 649), + CT abdomen.
3. Unfortunately: → sever SOB, hypoxia intubated → sever GI bleed → code status changed to comfort measures only → died

Summary and recommendations

- ✓ **Denosumab resulted in greater suppression of uNTx than IV BP, as evident by the significantly greater proportion of patients with uNTx lower than 50**
- ✓ **The effect of denosumab was rapid and appeared to be consistent regardless tumor types**
- ✓ **Denosumab was non-inferior (trending to superiority) to iv BP to control hypercalcemia of malignancy**
- ✓ **in pt malignancy associated hypercalcemia and concomitant Vit D deficiency who received high potent antiresorptive agents, maintenance vitD dose seems to be safe**

References

- Coleman RE: Skeletal complications of malignancy. Cancer 80:1588-1594, 1997
- Coleman RE: Metastatic bone disease: Clinical features, pathophysiology and treatment strategies. Cancer Treat Rev 27:165-176, 2001
- Berenson JR, Hillner BE, Kyle RA, et al: American Society of Clinical Oncology clinical practice guidelines: The role of bisphosphonates in multiple myeloma. J Clin Oncol 20:3719-3736, 2002
- Body JJ, Mancini I: Bisphosphonates for cancer patients: Why, how, and when? Support Care Cancer 10:399-407, 2002
- Hillner BE, Ingle JN, Chlebowski RT, et al: American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol 21:4042-4057, 2003
- Coleman RE, Major P, Lipton A, et al: Predictive value of bone resorption and formation markers in cancer patients with bone metastases receiving the bisphosphonate zoledronic acid. J Clin Oncol 23:4925-4935, 2005

Thank you

Milad Abusag MD

04/3/2014