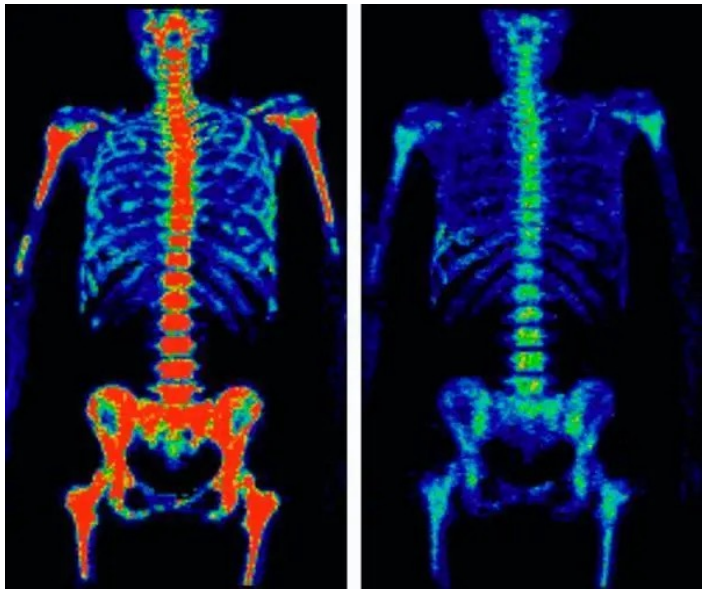

Management of Malignant Hypercalcemia and Bone Metastases

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Management of Malignant Hypercalcemia

Introduction

- Hypercalcemia is common in cancer patients, occurs 20-30%
- Occurs in both solid tumors and hematological malignancy patients
  - Most common breast, renal, lung, squamous cell carcinoma (SCC) and multiple myeloma
- Occurs late in the course of disease and portends a poor prognosis
- Mechanisms
  - Tumor secretion of parathyroid hormone-related protein (PTHrP)
  - Osteolytic metastases with release of cytokines (osteoclastic activating factors)
  - Tumor production of 1,25 dihydroxyvitamin D
  - Ectopic hyperparathyroidism

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

* PTH denotes parathyroid hormone, PTHrP PTH-related protein, $1,25(OH)_2D$ 1,25-dihydroxyvitamin D, and HTLV human T-cell lymphotrophic virus.

NEJM. Stewart A. 2005.

Hypercalcemia of Malignancy

Malignancies associated with hypercalcemia

Humoral hypercalcemia (secretion of PTHrP):
Squamous cell carcinomas
Renal carcinomas
Bladder carcinoma
Breast carcinoma
Lung cancer
Ovarian carcinoma
Prostate carcinoma
Colorectal carcinoma
Non-Hodgkin lymphoma
CML
Leukemia
Lymphoma
Osteolytic metastases:
Breast carcinoma
Multiple myeloma
Lymphoma
Leukemia
1,25-dihydroxyvitamin D:
Lymphoma (non-Hodgkin, Hodgkin, lymphomatosis/granulomatosis)
Ovarian dysgerminomas
Ectopic PTH secretion:
Ovarian carcinoma
Lung carcinomas
Neuroectodermal tumor
Thyroid papillary carcinoma
Rhabdomyosarcoma
Pancreatic carcinoma

PTHrP: parathyroid hormone-related protein; CML: chronic myeloid leukemia; PTH: parathyroid hormone.

Uptodate. Horwitz M. 2024

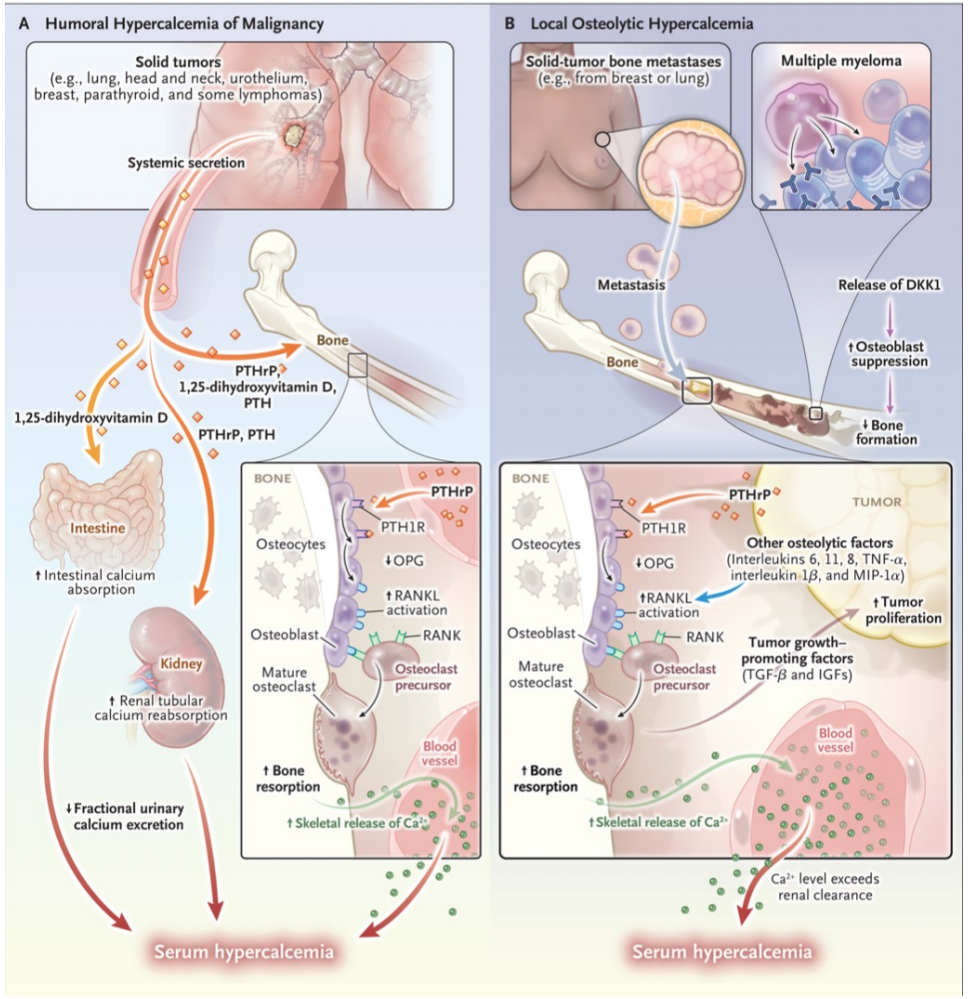
Mechanisms: PTH-related Protein

- Most common cause
- Known as humoral hypercalcemia of malignancy
- Evident in SCC (lung, head and neck), renal, bladder, breast and ovarian carcinomas
- PTHrP similar homology to PTH
  - First 13 amino acids almost identical, binds to the same receptor as PTH (bones and kidneys) and activates the same pathways --> Increased bone resorption, distal tubular calcium reabsorption and inhibition of proximal tubular phosphate transport
- Typical Lab Findings
  - Elevated PTHrP
  - Very low or suppressed serum intact PTH
  - Variable serum 1,25 dihydroxyvitamin D levels

Mechanisms: Osteolytic Metastases

- Accounts for 20% of hypercalcemia of malignancy
- Common with metastatic solid tumors and multiple myeloma
- Bone destruction mediated by osteoclasts and not a direct effect of tumor cells
  - Produce factors that stimulate osteoclast production --> increased skeletal resorption and hypercalcemia and suppress osteoblastic bone formation.
  - Calcium outflow from bone exceeds renal calcium clearance.
- Lab Findings
  - Low or suppressed serum intact PTH
  - Low or low-normal serum 1,25 dihydroxyvitamin D
  - Low or low-normal serum PTHrP
  - Extensive skeletal metastases or marrow infiltration

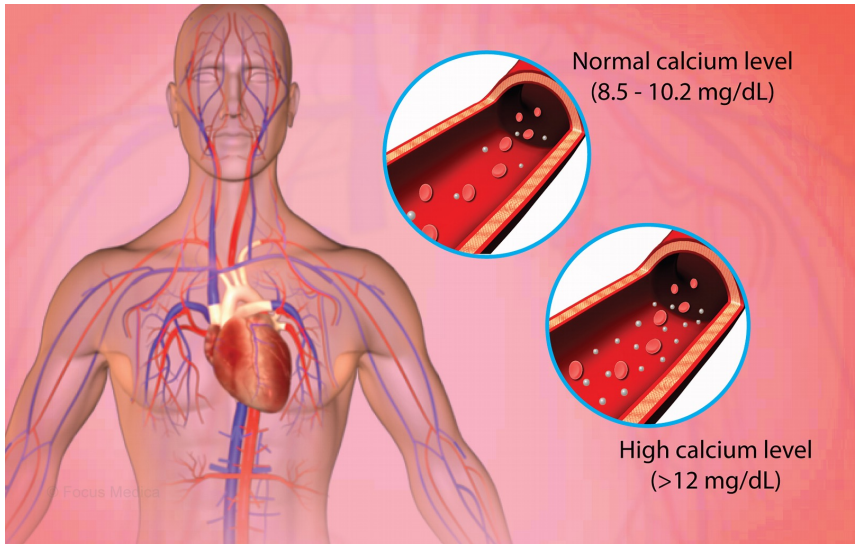
Pathophysiology of Humoral Hypercalcemia of Malignancy



NEJM. Guise T et al. 2022

Symptoms

- Clinical manifestations are nonspecific and related to the severity of the calcium levels or presence of bone metastasis.



- Mild serum calcium (SCa) <12 mg/dl
  - Fatigue, constipation and cognitive dysfunction
- Moderate SCa 12-14 mg/dl and Severe SCa >14 mg/dl
  - Polyuria, polydipsia and renal failure
  - Reduced quality of life, poor prognosis and hospitalization

Approach

- Asymptomatic or mildly symptomatic (<12 mg/dL)
  - Do not require immediate treatment
  - Avoid agents known to cause hypercalcemia
    - Thiazide diuretics, lithium, volume depletion, high calcium diet, calcium supplements etc.
- Symptomatic with SCa 12-14 mg/dL
  - May not require immediate treatment if chronic but if acute (marked changes in sensorium) will require immediate aggressive treatment
  - Treatment with saline hydration and bisphosphonates
- Symptomatic with SCa >14 mg/dL require aggressive treatment
  - Treatment with IV isotonic saline, subQ calcitonin (decrease in 12-48 hrs) and bisphosphonates

Table 2. Treatment Options for Cancer-Associated Hypercalcemia.*

Treatment	Mechanism	Dose	Expected Effect	Adverse Events	Comments
Intravenous fluids	Corrects volume deficit and induces calciuresis	Sodium chloride solution (0.9%) in initial bolus of 1–2 liters, followed by continuous intravenous infusion at 200–500 ml/hr	Lowers calcium by 1–1.5 mg/dl over first 24 hr	Volume overload	Adjust to urinary output of 100–150 ml/hr. Carefully assess for volume overload.
Furosemide	Acts through natriuresis-induced calciuresis	20–40 mg	Lowers calcium by 0.5–1.0 mg/dl after resolution of volume depletion	Potential volume depletion and worsening of hypercalcemia if volume not replete when initiated	Administer only after volume status restored. Particular benefit in patients at risk for volume overload.
Salmon calcitonin	Inhibits osteoclast activity	Subcutaneous or intramuscular infusion of 4–8 IU per kg of body weight every 8–12 hr for 48–72 hr	Rapidly lowers calcium by 1–2 mg/dl		Consider in patients with calcium level >15 mg/dl or altered consciousness. Tachyphylaxis may occur after 48–72 hr.
Pamidronate	Inhibits osteoclast activity, causes osteoclast apoptosis	Intravenous infusion of 60–90 mg over 2 hr in 50–200 ml of saline or 5% dextrose in water	Normalizes calcium in 60–70% of patients over 48–72 hr; median treatment duration of 11–14 days	Acute-phase response relatively common, with hypocalcemia especially likely if vitamin D deficiency present; renal insufficiency possible if administered in presence of decreased GFR or volume depletion or if administered too quickly; osteonecrosis of jaw and atypical femoral fractures possible but rare	Can be repeated every 2–3 wk. May cause kidney damage, especially if GFR <30–35 ml/min.
Zoledronate	Inhibits osteoclast activity, causes osteoclast apoptosis	Intravenous infusion of 4 mg over 15 min in 50 ml of saline or 5% dextrose in water	Normalizes calcium in 80–90% of patients over 48–72 hr, with median treatment duration of 30–40 days	Same as pamidronate; dose adjustment required if GFR <60 ml/min (see package insert)	Rehydrate before administration. Do not administer loop diuretics until patient is adequately rehydrated and use with caution in combination with zoledronate to avoid hypocalcemia (refer to package insert). Treatment can be repeated in 7 days if sufficient lowering of calcium level not achieved and every 3–4 weeks thereafter. May cause kidney damage, especially in patients with GFR <30–35 ml per minute.
Denosumab	Inhibits osteoclast formation, differentiation, and activity	Subcutaneous administration of 120 mg	Normalizes calcium in at least 70% of patients; median duration of response, 104 days	Acute-phase response less common than with bisphosphonates; osteonecrosis of jaw and atypical fractures rare. Rebound osteoclastogenesis may occur when denosumab discontinued without initiation of other therapy (e.g., bisphosphonate).	Not as well studied as bisphosphonates in cancer-associated hypercalcemia. Patients with GFR <30 have a higher risk of hypocalcemia, and a lower dose should be considered (see package insert). Can be given weekly for 4 wk, then monthly for maintenance.
Glucocorticoid	Inhibits 1-alpha-hydroxylase and lowers 1,25-dihydroxyvitamin D levels	Oral administration of 60 mg of prednisone per day for 10 days†	Has variable effects. Normalization of calcium levels possible if 1,25-dihydroxyvitamin D levels are significantly reduced. Response typically transient unless tumors are treated.	Hyperglycemia, altered mental status, hypertension, increased risk of infection and thromboembolism	Most commonly used in patients with lymphoma. Consider adding to bisphosphonate or denosumab in patients with humoral hypercalcemia and elevated circulating levels of 1,25-dihydroxyvitamin D.
Cinacalcet	Binds calcium-sensing receptor and inhibits secretion of parathyroid hormone in patients with parathyroid carcinoma and may increase renal calcium absorption through renal calcium-sensing receptor in nonparathyroid hypercalcemia	Oral administration of 30 mg per day initially. Can increase to 90 mg four times daily as needed to control hypercalcemia	Reduced calcium by at least 1 mg/dl in approximately 60% of patients with inoperable parathyroid carcinoma. Case reports of normalization of calcium in some nonparathyroid cancers in combination with other treatments.	Nausea, vomiting, headache, fractures	Approved for treatment of hypercalcemia related to parathyroid cancer. Case reports indicate reduction of calcium levels in patients with refractory hypercalcemia related to non–small-cell lung, neuroendocrine, breast, or renal cancer.
Dialysis	Removes excess calcium directly	Administration of low-calcium or calcium-free dialysate through peritoneal dialysis or hemodialysis	Transient reduction of calcium during dialysis		Can be useful initially in patients with severe chronic kidney disease or acute, life-threatening hypercalcemia.

* GFR denotes glomerular filtration rate.
† Other glucocorticoids may be used alternatively.

NEJM. Guise T et al. 2022

Treatment: IV hydration

- Hypercalcemia is associated with anorexia, nausea, vomiting and diabetes insipidus which lead to extreme dehydration and decreased GFR (decreases calcium excretion).
- First goal of treatment = correct fluid status
- Initial rate and duration of fluids should be determined based on clinical signs of dehydration, duration and severity hypercalcemia.
- Usually used concurrently with bisphosphonates with/without calcitonin
- Mode of action: restores intravascular volume and increases urinary calcium excretion
- Dose: 0.9% sodium chloride with initial dosage of 1-2L followed by IV infusion 200-500 ml/hr
- Onset: hours
- Duration of action: During infusion

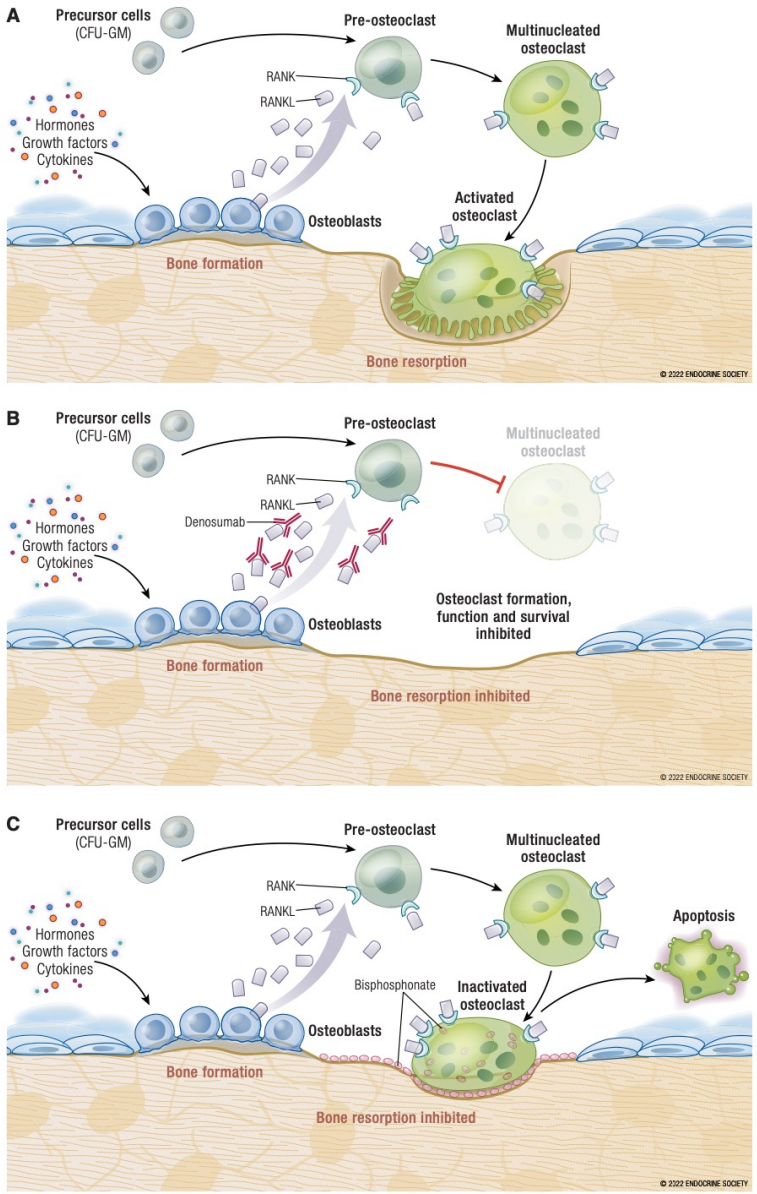
Antiresorptive Agents: Bisphosphonates

- Cancer associated hypercalcemia is a result of excessive bone resorption
- Pamidronate, zoledronate, clodronate and ibandronate (Europe) interfere with protein prenylation and inhibit osteoclast function by inducing apoptosis
- Dose: Zoledronic Acid 4 mg **preferred agent**, Pamidronate 60-90 mg IV
- Mode of action: inhibit bone resorption via interference with osteoclast recruitment and function.
- Onset: 24-72 hours
- Duration: 2-4 weeks
- Caution:
  - May worsen renal insufficiency and not recommended if severe volume depletion of <35 ml/min
  - Osteonecrosis of jaw and atypical femoral fractures

Antiresorptive Agents: Denosumab

- Fully human monoclonal antibody that binds to RANKL and prevents it from binding to receptor activator of nuclear factor κB on osteoclast precursors and mature osteoclasts --> inhibit formation, differentiation, activation and functioning of osteoclasts thus decreasing resorption
- Dose: Denosumab 120 mg SubQ
- Mode of action: Inhibits bone resorption via inhibition of RANKL
- Onset of action: 4-10 days
- Duration of action: 4-15 weeks
- Not renally excreted, useful in patients with renal insufficiency
- Caution: osteonecrosis of jaw and atypical femoral fractures

Osteoclast Activity



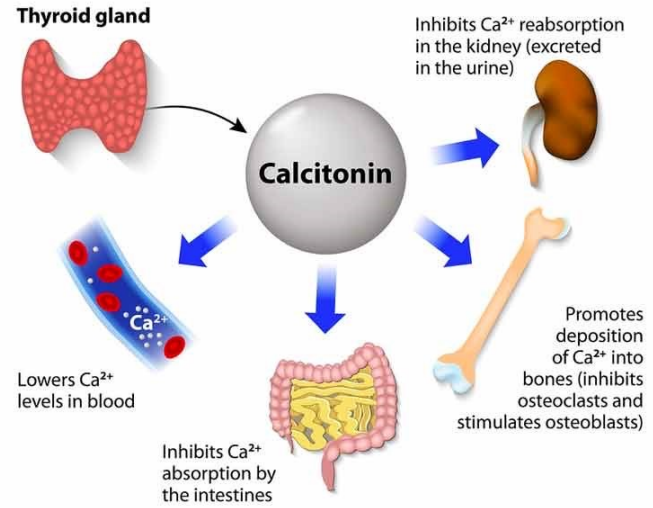
Bisphosphonates

Denosumab

Fuleihan G et al. Journal of Clinical Endocrinology & Metabolism. 2023.

Calcitonin

- Peptide hormone secreted by the parafollicular cells of the thyroid gland that inhibit osteoclast activity and promote renal calcium excretion
- Lower SCa levels rapidly within 12-24 hours and effects lost in 48-96 hours
  - Used as initial agent while awaiting antiresorptive agents to take effect
- Dose: SubQ or IM 4-8 IU/kg every 8-12 hours for 48-72 hours
- Mode of action: Inhibit bone resorption by interfering with osteoclast function. Promotes urinary calcium excretion.
- Onset: 4-6 hours
- Duration of action: 6-8 hours
- Caution: Tachyphylaxis may occur after 48-72 hours



Other treatments: Glucocorticoids

- Used in hypercalcemia associated with an overproduction of 1,25 dihydroxyvitamin D (lymphoma)
- Mode of action: Decreases intestinal calcium absorption and inhibits 1α-hydroxylase and limits 1,25-dihydroxyvitamin D production by mononuclear cells (granulomatous diseases or lymphoma)
- Dose: hydrocortisone 200-400 IV/day x 3-5 days or prednisone 60 mg PO/day x 10 days
- Duration of action: During treatment

Other treatments: Oral Calcimimetic agents

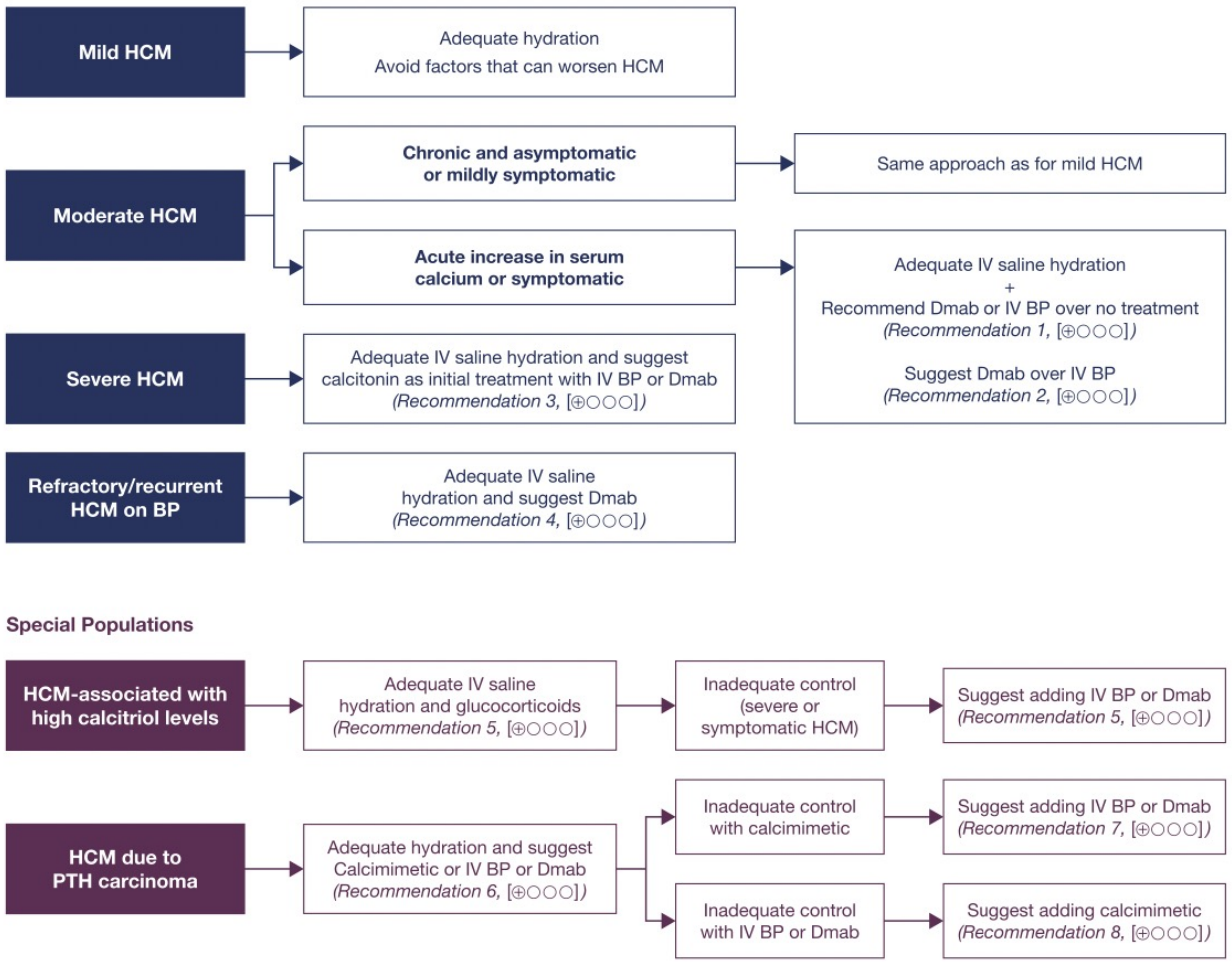
- Cinacalcet
  - Mode of action: Decreases PTH secretion and block renal tubular reabsorption of calcium by binding to the calcium-sensing receptors on the parathyroid glands and kidneys.
  - Dose: 30 mg/day, may increase incrementally every 2-4 weeks (60 mg BID, 90 mg BID and 90 mg 3-4x)
  - Onset of action: 2-3 days
  - Duration of action: During treatment

Refractory Hypercalcemia

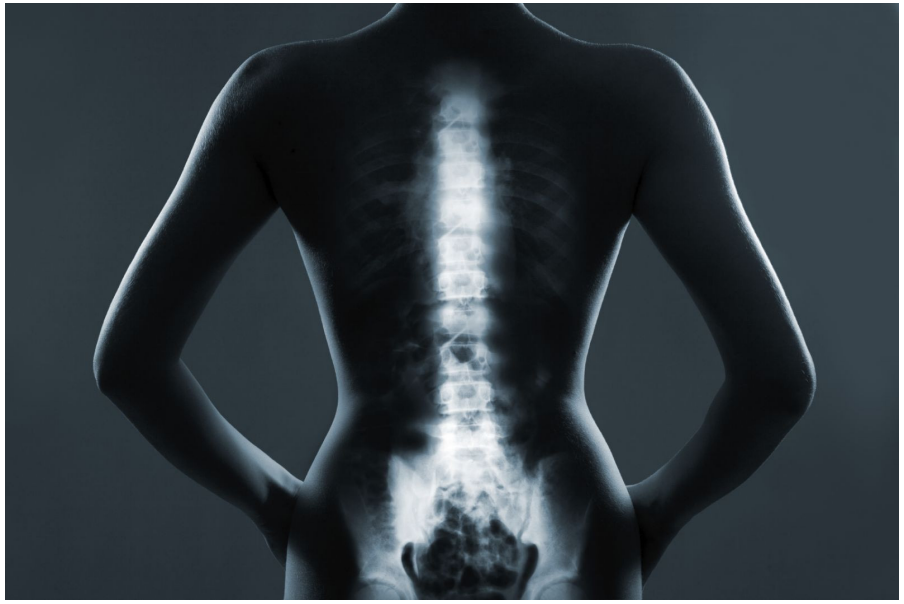
- Refractory to bisphosphonates, recommended to give denosumab 120 mg and may retreat in 2-7 days with additional 120 mg.

- Dialysis
  - Peritoneal or hemodialysis

Summary



Fuleihan G et al. Journal of Clinical Endocrinology & Metabolism. 2023.



Management of Bone Metastases

Introduction

- Common manifestation of distant relapse from many types of solid cancer (lung, breast and prostate)

- Skeletal related events (SREs) due to bone metastasis include pain, pathologic fractures, hypercalcemia and spinal cord compression.

- Goal of management
  - Maximize pain and symptom control
  - Preserving and restoring function
  - Minimizing risk for SRE
  - Stabilizing skeleton
  - Enhancing local tumor control

Treatments

- Supportive Care
  - Analgesia
  - Osteoclast Inhibitors
- Exercise
- Systemic anticancer therapy
- Local Treatment
  - Radiation
  - Surgery

Supportive Care

- Analgesia
  - Initial treatment is non-opioid pain medication
    - Acetaminophen
    - NSAIDs
  - Pain not adequately controlled, moderate to severe pain
    - Opioids
    - Glucocorticoids
- Osteoclast Inhibitors
  - Bisphosphonates
  - Denosumab

Osteoclast Inhibitors

- Indicated for metastatic bone disease for most patients with solid tumors
  - Exception Prostate Cancer: Benefits of osteoclast inhibitors were primarily seen only in metastatic castrate resistant prostate cancer
  - Patients with low-likelihood of SRE (minimal disease burden or limited survival (widespread/progressive, visceral metastasis) treatment should be considered on a case-by-case basis.
- Benefits
  - Slow or reverse the progression of skeletal metastatic disease
  - Decrease likelihood of SRE
  - Analgesic benefit (not 1st line)

Osteoclast Inhibitors

- Denosumab vs. Zoledronic Acid
  - Zoledronic acid can be given every 12 weeks vs. Zoledronic acid given every 4 weeks – breast and castrate resistant prostate cancer
  - Cost
  - Need for renal dosage reduction
  - SubQ vs. IV administration

Other treatment Modalities

- Exercise
  - Encouraged to engage in regular physical activity
    - Improves physical function
    - Decrease treatment related side effects
    - Decrease in cancer-related fatigue and psychosocial burden of living with cancer
- Systemic anticancer therapy
  - Systemic chemotherapy and/or hormonal therapy (aromatase inhibitors/antiestrogen)
  - Decreases tumor bulk and modulating pain signaling pathways
- Local Treatment
  - Surgery
  - Radiation

Take Home Points

- Degree of hypercalcemia and rate of rise of calcium determines symptoms and urgency of treatment
- Mild hypercalcemia (asymptomatic/mildly symptomatic) – no treatment
- Moderate (asymptomatic/mildly symptomatic) – chronic hypercalcemia (no treatment) or acute hypercalcemia (treatment)
- Severe hypercalcemia (regardless of symptoms) - treatment
- Treatment options:
  - IV hydration – isotonic saline
  - Bisphosphonates - IV zoledronic acid 4 mg IV (preferred)
  - Calcitonin – immediate/short term management, in combination with IV hydration and bisphosphonates
  - Denosumab – for refractory hypercalcemia/bisphosphonate contraindications
  - Dialysis – treatment refractory

It's bloodwork day, Bob.
Gotta take some blood!