Current Management of Metastatic Bone Disease

Evaluation and Medical Management

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Objectives

1. Outline an initial approach to the investigation of metastatic bone disease.

2. Discuss principles in the management of pain associated with metastatic bone disease.

3. Review guidelines and recommendations for bone-directed therapy.

4. Review the management of hypercalcemia in the setting of malignancy.
Metastatic Bone Disease: A Growing Concern

- Bone is one of the most common sites of distant metastases from cancer
- Prominent source of morbidity and major contributor to deterioration in QOL
- Significant healthcare burden, expected to increase in coming years as aging population develops malignancy
Detection and Diagnosis

- Imaging and investigations should be guided by clinical presentation and underlying malignancy
- Analgesia should be initiated (if required) while testing is planned or underway
Detection and Diagnosis - Labs

- CBC (potential marrow involvement)
- Electrolytes, including calcium
- Renal function
- Liver enzymes, including alkaline phosphatase
- Immunoglobulins, SPEP
Detection and Diagnosis - Imaging

- Plain films
- Skeletal survey
- Nuclear medicine bone scan
- CT
- MRI
- FDG-PET/CT
<table>
<thead>
<tr>
<th>Testing Characteristics</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plain films</td>
<td>44-50%</td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>75%</td>
<td>94%</td>
</tr>
<tr>
<td>Bone Scan</td>
<td>77%</td>
<td>83%</td>
</tr>
<tr>
<td>MRI</td>
<td>91%</td>
<td>96%</td>
</tr>
<tr>
<td>FDG-PET/CT</td>
<td>94%</td>
<td>97%</td>
</tr>
</tbody>
</table>
First presentation of malignancy?

- Complete staging to look for potential primary (CT CAP)
- Myeloma evaluation
- Consider biopsy
Role for Diagnostic Biopsy

• Consider a biopsy if:
  • History of cancer with no previous metastases
  • First presentation of cancer with no known or accessible primary
  • Solitary bone lesion
Goals of Management

- Maximizing pain control
- Preserving and restoring function
- Minimizing risk for skeletal-related events (SREs)
- Stabilizing the skeleton
- Enhancing local tumour control
Skeletal Related Events (SREs)

- Pain
- Pathologic fracture
- Hypercalcemia
- Spinal cord compression
- Need for radiation
Therapeutic Options

- Pain management/analgesia
- Bone-modifying agents (BMAs)
- Systemic anticancer therapy
- Radiation therapy
  - External beam
  - Stereotactic body radiation therapy (SBRT)
- Bone-targeting radiopharmaceuticals
- Surgery
- Image-guided thermal ablation
Pain Management/Analgesia

Adapted from World Health Organization. WHO’s Pain Ladder. 1986
CCO Symptom Assessment Tools

Pain Map: Pain in Cancer Patients

- **Mild Pain**
  - **Treatment with Non-Opioids**
    - Acetaminophen, adjuvant analgesics and NSAIDs should be considered at the lowest effective dose.
    - The need for ongoing or long term treatment should be reviewed periodically; if there is no significant response in one week drugs should be stopped.
    - Meperidine and pentazocine should not be used.
    - Long term use of NSAIDs requires gastric mucosa protection.
    - There is insufficient evidence to recommend bisphosphonates for bone pain management.

- **Moderate Pain**
  - **Treatment for Opioid Naive Patients**
    - Morphine starting dose is usually 5mg PO 4h with 2.5-5mg PO q1h pm for breakthrough pain. For elderly or frail patients, consider a starting dose of 2.5mg PO q4h.
    - Hydromorphone starting dose is 1mg PO q4h with 0.5 to 1mg PO q1h pm for breakthrough pain. For elderly or frail patients consider a starting dose of 0.5 mg PO q4h.
    - Oxycodone starting dose is 2.5 mg or one half tablet PO q4h, with 2.5 mg or one half tablet PO q1h pm for breakthrough pain. The lowest dose oxycodone tablets available, either in combination with acetaminophen or alone, contain 5mg of oxycodone. This is equivalent to approximately 5 to 10mg of oral morphine.

- **Severe Pain**
  - **Treatment for Opioid Naive Patients**
    - Oral: Morphine 5 to 10 mg PO q4h and 5mg PO q1h pm or hydromorphone 1 to 2 mg PO q4h and 1 mg PO q1 to q2h pm.
    - Subcutaneous/Intravenous: Morphine 2.5 to 5 mg SC/IV q4h & 2.5 mg q30min SC/IV pm or hydromorphone 0.5 to 1 mg SC/IV q4h & 0.5 mg SC/IV q30min pm.

- **Pain Crisis**
  - **Pain Crisis can occur at any time**.
    - A severe pain crisis requires prompt use of analgesics, adjuvant therapies, reassurance and a calm atmosphere.
    - Consider a consultation to palliative care or cancer pain specialist.
    - If IV access is present, and the person is opioid naive, give stat morphine 5 mg to 10 mg IV q10min until pain is relieved.
    - If IV access is present and the patient is taking oral opioids, convert the PO dose to IV, and administer IV q15min until pain is relieved. Monitor carefully.
    - If IV access is not present and the patient is opioid naive, give stat morphine 5-10 mg subcutaneous q20min until pain is relieved.
    - If IV access is not present, and the patient is opioid tolerant, convert the PO dose to subcutaneous, and administer q15min until pain is relieved. Monitor carefully.
    - Titrate dose by 25% every 1-2 doses until pain is relieved.
    - Do not try to manage a severe pain crisis with a long-acting opioid.

- **Treatment with Opioids (opioid naïve or opioid tolerant)**
  - For mild to moderate pain, a weak or lower potency opioid could be given in combination with a non-opioid analgesic.
  - If pain is not controlled with these combinations, go to "Moderate Pain - Treatment with Opioids".

- **Treatment with Opioids**
  - If the patient is taking an opioid...
    - Oral administration should be used over other routes.
    - As an immediate release preparation with q4h dosing, increase the regular and breakthrough doses by 25% from the starting dose. q24-q48h, if pain uncontrolled. Monitor side effects.
    - As a sustained release opioid, increase this dose by 25%. Change the breakthrough dose to 10% of the total 24h dose, either q1 to 2h pm PO or q30 min pm subcutaneous.
    - Make frequent assessments and adjustments to the opioid dose until the pain is better controlled.
    - Once patients have achieved stable pain and analgesic usage on oral morphine, oxycodone or hydromorphone, they should have their medication converted to a sustained or controlled release formulation given q1h for ease of administration. The short acting breakthrough dose is usually 10% of the total daily dose given at a frequency of q1 to 2h pm.
    - If pain is not well controlled despite multiple breakthrough doses, consider poor absorption, opioid induced hyperalgesia, or the need for adjuvants or non-pharmacologic interventions.

- **Treatment with Opioids**
  - If the patient is taking an opioid with q4h dosing, increase the regular and breakthrough doses by 25%. Ensure that the breakthrough doses are 10-15% of the daily dose. Ensure that the frequency of the breakthroughs are q1h pm if PO and q30min pm if subcutaneous.
  - If the patient is taking a sustained release opioid, increase this dose by 25%, and change the breakthrough doses accordingly.
  - Adjust the regular and breakthrough opioid dose every 24h to 48h to reflect the previous 24h total dose received.
  - If unmanageable opioid-limiting adverse effects are present (e.g. nausea, drowsiness, myoclonus), consult a palliative care service to assist with rotating to another opioid.
  - If there is difficulty getting the pain under control consider a consultation to palliative care.

Follow-up and ongoing monitoring should take place at all pain levels

If pain remains unresolved despite the approaches outlined above, request the assistance of a palliative care consultation team.
It takes a team!

If suboptimal control, seek help from:

• Palliative care team/consultant
• Oncology
• Interventional radiology
Bone-Modifying Agents

• Bisphosphonates
  • Structural analogs of inorganic pyrophosphate, inhibit osteoclastic bone resorption by attaching to hydroxyapatite binding sites in bone.

• RANK-ligand Inhibitor (Denosumab)
  • Fully human monoclonal antibody that inhibits osteoclastic bone resorption by binding and inhibiting RANK-ligand, a key regulator of osteoclast formation, function and survival.
Bone-Modifying Agents: Bisphosphonates

NEJM 2002; 346: 642
Bone-Modifying Agents

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Bone-Modifying Agents: Denosumab

Mechanism of action of denosumab

Factors stimulating bone resorption

RANKL

Denosumab binds to RANKL

Osteoclast formation, activity, and survival inhibited

RANK

Osteoclast formation, activity, and survival stimulated

Osteoblasts

Osteoclasts

RVH Royal Victoria Regional Health Centre

@TeamRVH Team RVH www.rvh.on.ca
Molecular Pathways of Bone Metastases

A. Physiological bone turnover/remodeling (normal)
- Tumor, dormant micro-metastasis
- Bone stromal cell
  - RANKL
  - Osteoblast
    - Bone formation
  - Osteoclast
    - Bone resorption
  - Homeostatic maintenance of bone mass

B. Tumor-induced pathologic bone turnover/remodeling (high)
- Tumor
  - Variety of tumor-derived factors
  - Tumor cell expressing RANKL
  - RANKL
  - Bone stromal cell
  - Increased bone formation
    - Mixed osteoblastic/osteolytic
  - Bone destruction (spectrum of lesions)
  - Osteoblasts
  - Increased bone resorption
  - Osteoclasts
  - Expanded tumor mass

Clin Cancer Res 2011; 18: 326-335
Bone-Modifying Agents

- Slow or reverse the progression of skeletal metastases
- Reduce the likelihood of SREs
- Modest analgesic benefit
### Bisphosphonates compared to placebo/observation for women with metastatic breast cancer with bone metastases

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>N# of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skeletal-related event (SRE)</strong></td>
<td>Study population</td>
<td>RR 0.86 (0.78 to 0.95)</td>
<td>2810 (9 RCTs)</td>
<td>High(^a)</td>
<td>Additional analyses of iv or oral bisphosphonates vs placebo showed equivalent efficacy</td>
</tr>
<tr>
<td>Follow-up: range 12 months to 24 months</td>
<td>640 per 1000</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>550 per 1000 (499 to 608)</td>
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<tr>
<td><strong>Median time to a skeletal-related event</strong></td>
<td>Bisphosphonates significantly delayed the median time to an SRE compared to placebo/observation (in 11 out of 12 studies that reported results but not sufficiently to be included in a meta-analysis). The median time to an SRE in the bisphosphonates group ranged from 8.7 to 20.8 months while the placebo group ranged from 4.9 to 14.9 months</td>
<td>Median ratio 1.43 (1.29 to 1.58)</td>
<td>2891 (9 RCTs)</td>
<td>High(^b)</td>
<td>Significant benefits were observed using iv bisphosphonates (7 studies) and oral bisphosphonates (4 studies) vs placebo</td>
</tr>
<tr>
<td>Follow-up: range 12 months to 24 months</td>
<td>575 per 1000</td>
<td>RR 1.01 (0.91 to 1.11)</td>
<td>1935 (7 RCTs)</td>
<td>Moderate(^b)</td>
<td>Analyses of iv or oral bisphosphonates vs placebo showed similar results</td>
</tr>
<tr>
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<td>581 per 1000 (523 to 638)</td>
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Indications for Bone-Modifying Agents

• Presence of metastatic bone disease for most patients with solid tumours and myeloma
• Majority of data extrapolated from studies in breast and prostate cancer
• The analgesic effect of BMAs are modest, and BMAs should not be used alone for bone pain
• Special considerations:
  • Minimal bone tumour burden
  • Limited expected survival
## Options for Treatment in Ontario

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Frequency</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic acid</td>
<td>4 mg IV</td>
<td>q3-4 weeks</td>
<td>CCO</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>4 mg IV</td>
<td>q12 weeks (breast and CRPC*)</td>
<td>CCO</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>90 mg IV</td>
<td>q3-4 weeks</td>
<td>CCO</td>
</tr>
<tr>
<td>Clodronate</td>
<td>1600 mg po</td>
<td>bid</td>
<td>ODB</td>
</tr>
<tr>
<td>Denosumab</td>
<td>120 mg subcut</td>
<td>q4 weeks</td>
<td>Not publicly funded</td>
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*CRPC = castrate resistant prostate cancer
Which is the best BMA?

- When compared to zoledronic acid, denosumab does have a modest superiority in SRE reduction, analgesic effect and can be administered subcutaneously.
- International guideline groups (ASCO, CCO and ESMO) have not expressed a preference for a particular agent.

Eur J Cancer 2012; 48: 3082
J Clin Oncol 2017; 35: 3978
Ann Oncol 2014; 25: 124-37
Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology–Cancer Care Ontario Focused Guideline Update

Optimal dosing interval for BMAs?

- Approved dosing schedule for zoledronic acid and pamidronate is q3-4 weeks, denosumab is q4 weeks

- Sufficient data in breast cancer, prostate cancer and myeloma to support q12 week dosing for zoledronic acid

- Insufficient data to recommend a change in dosing interval for bone metastases from other solid tumours

- Insufficient data to support q12 week dosing for denosumab, but studies underway
Optimal duration of treatment for BMAs?

• Guidelines suggest to continue treatment indefinitely in absence of excessive toxicity, as long as consistent with goals of care

• Clinically significant impact on SREs requires at least 6 months of treatment

BMJ 2003; 327: 469.
## Complications

<table>
<thead>
<tr>
<th>Bisphosphonates</th>
<th>Denosumab</th>
</tr>
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<tbody>
<tr>
<td>- Osteonecrosis of the jaw</td>
<td>- Possible increased risk infection</td>
</tr>
<tr>
<td>- Hypocalcemia</td>
<td></td>
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<tr>
<td>- Other electrolyte abnormalities</td>
<td></td>
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<tr>
<td>- Atypical fractures</td>
<td></td>
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<tr>
<td>Renal insufficiency</td>
<td></td>
</tr>
<tr>
<td>Acute phase responses</td>
<td></td>
</tr>
<tr>
<td>Ocular toxicities</td>
<td></td>
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<tr>
<td>Musculoskeletal pain</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
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Osteonecrosis of the Jaw (ONJ)

- Overall risk is <2% in patients receiving BMAs in the first year
- Risk rises with prolonged therapy
- Risk of ONJ slightly higher with denosumab than bisphosphonates (1.9 vs 1.3% in the first year)
- Dental surgery is a major risk factor, assessment prior to initiating treatment recommended
- Invasive dental procedures should be avoided if possible
- If a dental procedure is required, BMA should be held for 8-12 weeks if possible

J Clin Oncol 2011; 29: 1221
MRONJ 2014 Update: American Association of Maxillofacial Surgeons
Bone-Modifying Agents

- Selection based on:
  - Tumour type
  - Patient preference
  - Route of administration
  - Frequency of administration
  - Tolerance
  - Cost of therapy and coverage
Osteoclast inhibitors for patients with bone metastases from solid tumors

All patients:  
- Dental evaluation, assess calcium and vitamin D intake, and advise supplements as necessary

Breast cancer or CRPC

Select denosumab or zoledronic acid based on patient and clinician preference, route and frequency of administration, and cost (refer to UpToDate text)

Zoledronic acid

CRPC

Dosing every 4 or 12 weeks; continue indefinitely

Breast cancer

Extensive bone disease and/or highly symptomatic?

Yes

Initiate therapy with dosing every 4 weeks

Switching to dosing every 12 weeks after >9 months is an option for stable bone disease; continue indefinitelyΔ

No

Initiate therapy once every 4 weeks

Denosumab

Subcutaneous denosumab 120 mg every 4 weeks; continue indefinitely

Other solid tumor

Select drug of choice:
- Denosumab may be favored for some patients
- Bisphosphonates are an acceptable alternative (refer to UpToDate text)*

Denosumab

Dosing every 4 weeks; continue indefinitely

Zoledronic acid

Initiate zoledronic acid with dosing every 4 weeks; bisphosphonate therapy should be continued indefinitely†
# Bone-Modifying Agents: Comparison

<table>
<thead>
<tr>
<th></th>
<th>Zoledronic Acid</th>
<th>Denosumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Route of administration</strong></td>
<td>IV</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td><strong>Frequency of administration</strong></td>
<td>q3-4 weeks or q12 weeks</td>
<td>q4 weeks</td>
</tr>
<tr>
<td><strong>Toxicity Considerations</strong></td>
<td>Renal impairment, Acute phase response</td>
<td>Hypocalcemia</td>
</tr>
<tr>
<td><strong>Cost of therapy</strong></td>
<td>Covered by CCO</td>
<td>Private insurance</td>
</tr>
</tbody>
</table>
Hypercalcemia

- Occurs in up to 20-30% of patients with cancer at some time during the course of their disease
- Occurs in both solid tumours and hematologic malignancies
- Most commonly associated with breast cancer, RCC, lung cancer and myeloma
- Often associated with a poor prognosis
Hypercalcemia: Clinical Manifestations

* Bones, Stones, Moans and Groans*
  - **Renal** (polyuria, polydipsia, stones, insufficiency/failure)
  - **GI** (anorexia, n/v, constipation)
  - **MSK** (muscle weakness, pain)
  - **Neurologic** (confusion, fatigue, coma)
  - **Cardiovascular** (arrhythmia, HTN)
## Hypercalcemia: Mechanisms

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency (%)</th>
<th>Bone Metastases</th>
<th>Causal Agent</th>
<th>Typical Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local osteolytic hypercalcemia</td>
<td>20</td>
<td>Common, extensive</td>
<td>Cytokines, chemokines, PTHrP</td>
<td>Breast cancer, multiple myeloma, lymphoma</td>
</tr>
<tr>
<td>Humoral hypercalcemia of malignancy</td>
<td>80</td>
<td>Minimal or absent</td>
<td>PTHrP</td>
<td>Squamous-cell cancer, (e.g., of head and neck, esophagus, cervix, or lung), renal cancer, ovarian cancer, endometrial cancer, HTLV-associated lymphoma, breast cancer</td>
</tr>
<tr>
<td>1,25(OH)₂D-secreting lymphomas</td>
<td>&lt;1</td>
<td>Variable</td>
<td>1,25(OH)₂D</td>
<td>Lymphoma (all types)</td>
</tr>
<tr>
<td>Ectopic hyperparathyroidism</td>
<td>&lt;1</td>
<td>Variable</td>
<td>PTH</td>
<td>Variable</td>
</tr>
</tbody>
</table>

NEJM 2005; 352: 373-379
Mild Hypercalcemia: Treatment

- Serum calcium level <3 mmol/L
- Does not require immediate treatment
- Eliminate contributing factors:
  - Calcium supplementation
  - Medications (thiazide diuretics, lithium)
  - Inactivity
  - Volume depletion
- Hydration (6-8 glasses water/day)
Moderate Hypercalcemia: Treatment

- Serum calcium level 3-3.5 mmol/L
- Symptoms will depend on rate of increase of serum calcium (patients with chronically elevated levels may be asymptomatic)
- Urgency of treatment depends on symptoms
Severe Hypercalcemia: Management

1. Hydration or calciuresis
   - Intravenous saline
   - Furosemide

2. First-line medications
   - IV bisphosphonates (zoledronic acid superior to pamidronate)
   - Denosumab

3. Second-line medications
   - Glucocorticoids
   - Calcitonin

4. Hemodialysis

Summary

- Bone metastases are common in patients with malignancy and can lead to significant symptoms and deterioration of QOL
- Pain management should be initiated once suspected, while investigations are underway
- Bone-modifying agents reduce SREs and should be considered for most patients with bone metastases, regardless of primary
- Consider hypercalcemia as a cause for symptoms (pain, confusion, abdominal pain, renal failure) and manage promptly