Bone metastases of solid tumors
Diagnosis and management
by
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Nasser institute adult oncology unit
Goals

• 1- Know the multitude of problem of bone metastases
• 2- Explain theories for the mechanism of bone metastases.
• 3- Explain theories for the mechanism of bone pain.
• 4- Management of bone metastases
• 5- Complications of bone metastases and their management.
The exact incidence of bone metastases is difficult to determine, but estimates are that more than 100,000 people in the United States will develop osseous metastatic disease annually.

Bone metastases may be found in up to 85% of patients dying from breast, prostate, or lung cancer.

Pereze 2008
Survival of patient with bone metastases

• The ultimate **prognosis** for patients with bone metastases is poor, with median survival typically **measured in months rather than years**

• **Overall survival** depends on the **primary site** and the presence or absence of visceral metastases. Patients with bone metastases from lung cancer have short median survival durations of 6 months.

• However, patients with bone metastases from **breast or prostate primary sites** may have significantly longer **survival times**. In patients with bone-only metastatic prostate or breast cancer, median survivals of 2 to 4 years have been reported.
Bone metastasis leads to a complex cellular and molecular ecosystem with the involvement of a multitude of cells:

1- Cancer cells
2- Stromal cells.
3- Osteoclasts.
4- Inflammatory cells.
Roato et al 2005 concluded that:

there is a spontaneous osteoclastogenesis
in patients affected by solid tumors
with metastatic osteolysis.

and that osteoclastic activity is an early
and important response to tumor cell
invasion of bone.
Spontaneous osteoclastogenesis in cancer patients: D, E, and F in comparison with controls: A, B, and C and treated by M-CSF,
Theories of PAIN

Pain from bone metastases explained by direct stimulation of afferent nerve fibers that are stimulated by mechanical injury.

or by multitude of factors present in the complex micro-environment of bone metastases.

Local tissue acidosis is the hallmark physiologic response to injury and inflammation and the degree of pain is correlated with the magnitude of acidification. (Chow et al 2002).
Origin of pain from bone metastases. (Vakate and Boterberg 2004)

POSSIBLE LOCAL MECHANISMS OF INDUCING BONE PAIN

- Release of chemical mediators
- Increased pressure within the bone
- Microfractures
- Stretching of the periosteum
- Reactive muscle spasm
- Nerve root infiltration
- Compression of the nerves due to collapse of the bone
Evaluation of Patients with Unexplained Musculoskeletal Pain

Adult patient with musculoskeletal pain

Pain at rest?

No

Consider non-neoplastic causes (e.g., arthritis)

Yes

Radiography, including nearby joints

Suspicous lesion?

No, but pain persists

Whole-body bone scan

Unexplained lesions?

No

Consider non-neoplastic causes (e.g., arthritis)

Yes

Metastatic work-up: Computed tomography of chest, abdomen, and pelvis plus laboratory evaluation

Primary carcinoma discovered?

No

Refer for biopsy of possible primary bone tumor

Yes

Proximal femoral lesion?

No

Refer for medical and radiation oncology

Yes

Refer for possible prophylactic surgical fixation
Diagnosis of bone metastases

• 1-Plain X ray
• 2- Bone scan
• 3- CT examination
• 4- MRI
• 5-PET scan
• 6- OTHRS
Plain x ray can be enough for diagnosis
Sclerotic bone metastases inpatient with SCLC
From left to right: CT appearance of vertebral metastases, PET scan of the same vertebral metastases and the fusion of the CT and PET scan for the same metastases. (Even 2005)
Bone scan of a female patient with breast cancers showing increase uptake in sternum but PET scan of the same patient show increase uptake in the whole skeleton mainly in humerus and femur. (Abe et al 2005)
• MRI and PET scan for bone metastases showing sites of disease
Problems during practice
• 1-These skeletal metastases can require **surgery and/or radiotherapy to bone**, in addition to **aggressive analgesic therapy and systemic therapy**.

• 2- Furthermore, bone metastases have a major impact on the **quality of life and even survival of these patients** *(Silberstein 2005)*

• 3- Bone metastases is responsible for some of the most devastating complications of malignancy, including **pathologic fractures, spinal cord compression syndromes, bone pain, and hypercalcemia**.
Effect of Radiation Therapy on bone metastases
The vicious circle of bone metastases thick blue arrows pain pathway in green arrow and radiation induced apoptotic death in red arrows. (Munday 2002)
Effect of RTH (1)

Although treatment by EBRT is successful in most patients the exact mechanism of action is unknown. Inflammatory cells are obvious candidates because of the inhibition of chemical mediators, other candidates are osteoclasts.
Effect of RTH (2)

– It has been demonstrated by Hoskin et al 2000 that there is decrease in urinary DPD after RTH which means that there is an effect on osteoclastic activity. Also there was a clear dose-response relationship between doses of RTH and osteoclast number in vitro was observed by Tsay et al 1995
# Follow up response of therapy for bone metastases

Table 2. Bone formation and resorption markers used for assessing response in metastatic bone disease from breast cancer

<table>
<thead>
<tr>
<th>Bone formation markers</th>
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<tbody>
<tr>
<td>Bone-specific alkaline phosphatase</td>
</tr>
<tr>
<td>Osteocalcin</td>
</tr>
<tr>
<td>PINP, PICP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bone resorption markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary calcium excretion</td>
</tr>
<tr>
<td>Urinary hydroxyproline</td>
</tr>
<tr>
<td>Collagen pyridine cross-links (PYD, DPD)</td>
</tr>
<tr>
<td>Protein-bound cross-links (NTx, CTX/ICTP)</td>
</tr>
</tbody>
</table>

Abbreviations: CTX/ICTP, C-terminal cross-linked type I collagen telopeptide; DPD, deoxypyridinoline; NTx, N-terminal cross-linked type I collagen telopeptide; PICP, C-terminal propeptide of procollagen type I; PINP, N-terminal propeptide of procollagen type I; PYD, pyridinoline.
Authors hypothesize that there are two mechanisms could explain the changes in resorption activity after RTH:

1- Interference with the enzymatic process involved in the resorption of cartilage matrix and mineral.

2- Alternation in the mobility of osteoclasts.

(Vakaet and Boterberg 2004)
Radiation therapy dose

- **highest doses** — 4050 cGy (solitary metastases) and 3000 cGy (multiple metastases) — provide the highest rate of combined complete relief (pain score and narcotic score) and are significantly better than the alternate regimens.

- **For most patients who achieve pain relief lasts for less than two third of their remaining life.** In most series, 10% to 30% of patients never obtain relief.
RTH dose

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- For most patients who achieve pain relief lasts for less than two third of their remaining life. In most series, 10% to 30% of patients never obtain relief (Ramusson et al 1995).
Wide field irradiation

The best result of himi-body irradiation of painful bone metastases considering histopathological diagnosis, was in multiple myeloma (100% pain relief), prostate cancers (the average degree of 78%) and lung cancers (88%). Taking to account type of metastases the best result was obtained in the cases of osteolytic metastases.
Re treatment

- Even if re-treatment is more frequently given after a single fraction radiation, a few short visits may still be more preferable for many patients than a protracted treatment course up front without compromising the goal of alleviating symptoms.

- Periz 2008.
• **The clinical effect** is assessed by assessment of pain scale, analgesics use, mobility and performance status before treatment and after two, four and six weeks of radiotherapy.

• **The biological effect** is assessed by evaluation of bone resorption marker DPD in urine of the patients before treatment and after six weeks of radiation therapy.
Type of fractionation

single fraction radiotherapy appears to be as effective as multiple fractions in the three large randomized trials; Dutch bone metastases study group (Steenland et al 1999), Bone Pain Trial Working Party 1999, and Radiation Therapy and Oncology study Group RTOG (Harstell et al 2005)
Bone metastasis emergencies

- Bone pain
- Bone fracture
- Impending fracture
- Spinal cord compression
- Others
Impending fracture

Clinically the size of metastases is calculated from orthogonal radiographs.

Number of studies have shown that pathological fracture can occur in patients with lesions that exceed 50% of bone diameter others have shown that a lesion larger than 2.5 cm are more likely to fracture than lesions less than 2.5 cm.
Table 1. Mirels Scoring System for Pathologic Fracture Risk

<table>
<thead>
<tr>
<th>Variable</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>Upper limb</td>
<td>Lower limb</td>
<td>Peritrochanter</td>
</tr>
<tr>
<td>Pain</td>
<td>Mild</td>
<td>Moderate</td>
<td>Activity-related</td>
</tr>
<tr>
<td>Lesion type</td>
<td>Blastic</td>
<td>Mixed</td>
<td>Lytic</td>
</tr>
<tr>
<td>Size</td>
<td>Less than one third of the</td>
<td>One to two thirds of the</td>
<td>More than two thirds of the</td>
</tr>
<tr>
<td></td>
<td>cortical diameter</td>
<td>cortical diameter</td>
<td>cortical diameter</td>
</tr>
</tbody>
</table>

NOTE: A score of 7 or less indicates that the patient should be treated with radiation only; a score of 8 or more indicates that the patient should undergo prophylactic surgical fixation.

Plain x ray

Radiographs of the entire long bone must be obtained for all painful sites; these should be carefully inspected for the type and extent of disease.

- Multiple lesions are a characteristic feature of metastatic disease.
Fixation of impending fracture
Patel and DeGroot 2001 added some points to the total score:

- for any lesion in the femur proximal to the lesser trochanter,
- a lesion in the proximal half of the humerus,
- patient with breast cancer,
- patient who did not receive bisphosphonate treatment,
- and presence of osteoporosis
Aim of Surgical Management of pathologic fracture

The goals of surgical intervention are:

1- To prevent or relieve pain,
2- Improve motor function,
3- To improve overall quality of life
Factors to be considered before decision of surgical fixation

1-estimated risk of pathologic fracture.
2-limited life span,
3-diagnosis (primary site),
4-performance status,
5-number of bone metastases,
6-presence of visceral metastases,
7-hemoglobin level.

*J Clin Oncol 2005;23:6072–6082*
Spinal cord compression
Spinal cord compression constitutes a true emergency because the initial injury to the spinal cord will lead to:

permanent loss of neurologic function if the pressure of the tumor on the cord is not relieved quickly.
Prognosis depends on

- length of time of the cord impingement,
- the location of the mass in the spinal column
- the tissue type of the mass.
- the functional status
- length of survival after treatment.
Tokuhashi et al. 1990 proposed a preoperative prognostic scoring system

• 1. General condition
• 2. Number of extra-spinal bone metastases
• 3. Number of metastases in the spine
• 4. Metastases to major internal organs
• 5. Primary site of cancer
• 6. Myelopathy
Results of a Selection of Recent Series of Patients Surgically Treated for Spinal Metastases Followed by Radiotherapy and/or Other Forms of Adjuvant Therapy

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Huang, 2006&lt;sup&gt;80&lt;/sup&gt;</th>
<th>Hirabayashi, 2002&lt;sup&gt;81&lt;/sup&gt;</th>
<th>Holman, 2005&lt;sup&gt;82&lt;/sup&gt;</th>
<th>Villavicencio, 2005&lt;sup&gt;83&lt;/sup&gt;</th>
<th>North, 2005&lt;sup&gt;84&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (mf)</td>
<td>46 (28/18)</td>
<td>81 (58/23)</td>
<td>139 (85/54)</td>
<td>58 (?)</td>
<td>61 (34/27)</td>
</tr>
<tr>
<td>Neurological improvement</td>
<td>?†</td>
<td>49.4%</td>
<td>41%</td>
<td>60%</td>
<td>?</td>
</tr>
<tr>
<td>Neurological impairment</td>
<td>0%</td>
<td>1.2%</td>
<td>5%</td>
<td>3.4%</td>
<td>8.1%</td>
</tr>
<tr>
<td>Ambulatory preoperatively</td>
<td>29.6%‡</td>
<td>38.3%</td>
<td>71.9%</td>
<td>58.6%</td>
<td>85%</td>
</tr>
<tr>
<td>Ambulatory postoperatively</td>
<td>76.1%</td>
<td>71.3%</td>
<td>90.6%</td>
<td>77.5%</td>
<td>96.7%</td>
</tr>
<tr>
<td>Preoperative pain; number (%)</td>
<td>?</td>
<td>63 (79%)</td>
<td>133 (96%)</td>
<td>53 (92%)</td>
<td>59 (97%)</td>
</tr>
<tr>
<td>Postoperative complete or partial relief of pain</td>
<td>?</td>
<td>77%</td>
<td>96%</td>
<td>92.9%</td>
<td>56%</td>
</tr>
<tr>
<td>Complications (major)*</td>
<td>19.5% (8.7%)</td>
<td>23.5% (12.3%)</td>
<td>32.4% (12.9%)</td>
<td>20.6% (10.3%)</td>
<td>11.4% (4.9%)</td>
</tr>
<tr>
<td>Survival</td>
<td>Mean</td>
<td>Median</td>
<td>Median</td>
<td>Mean</td>
<td>Median</td>
</tr>
<tr>
<td></td>
<td>26.4 months</td>
<td>10.6 months</td>
<td>14.8 months</td>
<td>13 months§</td>
<td>10 months</td>
</tr>
</tbody>
</table>
Local treatment only is never enough
Systemic treatment for bone metastases
Radiotherapy is the main palliative local treatment for patients with painful bone metastases:

- Systemic treatments include:
  - Pain killers radiopharmacotherapy, bisphosphonates, chemotherapy, hormonal therapy.

The use of both local and systemic therapy is recommended for most patients with bone metastases.
Bisphosphonates
Bisphosphonates: Mechanism of Action

- Antiresorptive agents
- Bind to hydroxyapatite crystals in bone
- Directly or indirectly inhibit osteoclasts
- Inhibit bone mineralization (at sufficient doses)
- Pharmacologically active only while on exposed bone surfaces
  - Remains bound in bone matrix for years
The main goal for use of bisphosphonates in the reduction of SRE

Skeletal related events generally includes:
Pathological vertebral fractures
Pathological non-vertebral fractures
Spinal cord compression
Surgery for bone complications
Radiotherapy for bone complications
Hypercalcaemia

Does not include
Pain
Immobility
Analgesic use
Non-hospital costs (physiotherapy)
## Bisphosphonates and SRE

<table>
<thead>
<tr>
<th>Agent and route</th>
<th>N</th>
<th>Results</th>
<th>Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clodronate 1600 mg po vs placebo</td>
<td>173</td>
<td>Reduced SMR – 305 vs 219 events/100 woman years (P = &lt;0.001)</td>
<td>Paterson</td>
</tr>
<tr>
<td>Pamidronate 45 mg IV vs control</td>
<td>295</td>
<td>Increased time to bone progression – 168 vs 249 days (P = 0.02)</td>
<td>Conte</td>
</tr>
<tr>
<td>Pamidronate 90 mg IV vs placebo</td>
<td>382</td>
<td>Reduced proportion experiencing SRE – 65% vs 46% (P = &lt;0.001)</td>
<td>Hultborn</td>
</tr>
<tr>
<td>Pamidronate 60 mg IV vs control</td>
<td>401</td>
<td>Median time to skeletal progression – 9 vs 14 months (P = &lt;0.01)</td>
<td>Theriault</td>
</tr>
<tr>
<td>Pamidronate 90 mg IV vs placebo</td>
<td>374</td>
<td>Reduced proportion experiencing SRE – 67% vs 56% (P = 0.027)</td>
<td></td>
</tr>
<tr>
<td>Ibandronate 2/6 mg IV vs placebo</td>
<td>467</td>
<td>Reduced SMR with 6 mg dose, 2 mg ineffective – SMR 2.18 vs 1.61 (P = 0.03)</td>
<td>Body</td>
</tr>
<tr>
<td>Zoledronic acid 4 mg iv vs placebo</td>
<td>227</td>
<td>Reduced proportion experiencing SRE – 50% vs 30% (P = 0.003)</td>
<td>Kohno</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduced SMR by 43% (P = 0.016)</td>
<td></td>
</tr>
<tr>
<td><strong>Multiple myeloma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clodronate 1600 mg po vs placebo</td>
<td>350</td>
<td>Improved 2-year progression-free survival – 24 vs 12% (P&lt;0.05)</td>
<td>Lahtinen</td>
</tr>
<tr>
<td>Pamidronate 90 mg IV vs placebo</td>
<td>392</td>
<td>Reduced proportion experiencing SRE – 24% vs 41% (P&lt;0.001)</td>
<td>Berenson</td>
</tr>
<tr>
<td>Clodronate 1600 mg po vs placebo</td>
<td>614</td>
<td>Less skeletal morbidity and pain on progression</td>
<td>McCloskey</td>
</tr>
<tr>
<td><strong>Prostate cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clodronate (4 × 520) mg oral vs placebo</td>
<td>311</td>
<td>Reduction in number of SREs vs placebo not significant – 49 vs 41%, (P = NS)</td>
<td>Dearmaley</td>
</tr>
<tr>
<td>Pamidronate 90 mg iv vs placebo</td>
<td>378</td>
<td>Number of SREs equal in pamidronate and placebo-arms, (P = 1.0)</td>
<td>Small</td>
</tr>
<tr>
<td>Zoledronic acid 4/8 mg vs placebo</td>
<td>643</td>
<td>25% reduction in proportion of patients experiencing at least one SRE – (P = 0.021)</td>
<td>Saad</td>
</tr>
<tr>
<td><strong>Other tumour types</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid 4/8 mg vs placebo</td>
<td>773</td>
<td>Significant delay to time of rst SRE (P = 0.023)</td>
<td>Rosen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduction in proportion of patients with SRE – 47 vs 38%, (P = 0.039)</td>
<td></td>
</tr>
</tbody>
</table>
Different types with different potency and mechanism of action

BP compounds are remarkably variable in structure and resulting physicochemical and biological properties, including potency.

Nitrogen-containing bisphosphonates (N-BP) such as ibandronate (IBA), pamidronate (PAM), risedronate (RIS), and zoledronic acid (ZOL) are several orders of magnitude more potent than earlier generation BP such as: etidronate, tiludronate and clodronate (CLO).

N-BP interfere with cell signalling and block the prenylation of small signalling proteins (e.g. Ras, Rho) which are essential for cell function and survival.

While non-N-BP are incorporated into adenosine triphosphate (ATP)-containing compounds, thus inhibiting cell function,
Clinical trials of bisphosphonates to prevent metastasis
British Journal of Cancer (2008) 98(11), 1736 – 1740

<table>
<thead>
<tr>
<th>Agent and trial descriptor</th>
<th>Setting</th>
<th>Treatment and duration</th>
<th>Study size and status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clodronate (oral)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSABP-B34</td>
<td>Stage I–III breast cancer</td>
<td>3 years clodronate vs placebo</td>
<td>3400</td>
</tr>
<tr>
<td><strong>Zoledronic acid (i.v.)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZURE</td>
<td>Stage I–III breast cancer</td>
<td>5 years zoledronic acid vs control</td>
<td>3360</td>
</tr>
<tr>
<td>Z-FAST/ZO-FAST/EZO-FAST</td>
<td>Stage I–III breast cancer</td>
<td>Immediate vs delayed zoledronic acid</td>
<td>2193</td>
</tr>
<tr>
<td>ABCSG XII</td>
<td>Stage I–III breast cancer</td>
<td>6 monthly zoledronic acid vs control</td>
<td>1800</td>
</tr>
<tr>
<td>SUCCESS</td>
<td>Stage I–III breast cancer</td>
<td>3 vs 5 years zoledronic acid</td>
<td>3754</td>
</tr>
<tr>
<td>ZEUS</td>
<td>High-risk prostate cancer</td>
<td>3 years zoledronic acid vs control</td>
<td>1433</td>
</tr>
<tr>
<td>2419</td>
<td>Stage II/III NSCLC</td>
<td>2 years zoledronic acid vs control</td>
<td>446</td>
</tr>
<tr>
<td><strong>Ibandronate (oral)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAIN</td>
<td>Stage I–III breast cancer</td>
<td>2 years ibandronate vs control</td>
<td>&gt;3000</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S0307/Intergroup</td>
<td>Stage I–III breast cancer</td>
<td>3 years clodronate vs zoledronic acid vs ibandronate</td>
<td>4500</td>
</tr>
</tbody>
</table>
In breast cancer, an N-BP is preferably offered to patients with MBD. Generally, i.v. administration is preferable; however, oral administration should be considered for patients who cannot or do not have to attend regular hospital care.
• Before starting N-BP treatment, patients should have a dental examination and appropriate treatment and should be advised to maintain good oral hygiene.

• *It is finally recommended to consider the use of calcium (1 g/day) and vitamin D3 (800 IU/day) whenever BP are used*
Calcium and vitamin D3 should be considered from the start of therapy with BP.

In patients with renal impairment receiving i.v. BP, lower doses, longer infusion times, and selecting a BP with best possible renal tolerability.
Duration of treatment

• Since the risk of SREs (skeletal related events) is continuous, the expert panel recommends continuing treatment until 2 years, even if a patient experiences a bone event. (ESMO 2008)
With the repeated use of bisphosphonates we should consider their osteonecrotic effect on the mandible and the late renal effect. This picture shows the osteonecrosis of the right posterior mandible of a patient after the repeated use of zolodrinic acid. (Melo and Obed 2005)
Summary And Conclusion
• **Bone metastases is one of the major problems in cancer patients.**

• **Evaluation of patient with bone metastases needs exclusion of complications.**

• **The main treatment of bone metastases is radiation therapy**

• **Decision of surgery needs oncology committee.**

• **Systemic treatment should be considered for all patients with bone metastases.**
The goal of management is palliation

improvement of quality of life:

is defined as an individual's overall satisfaction with life and general sense of personal well-being
Thank You