Management of metastatic, recurrent and intractable breast cancer

Nursing Care in Bone Metastasis

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Hyejin Cho, RN, OCN.
I. Bone Metastasis in Breast Cancer

II. Process

III. Complication

IV. Imaging modality

V. Treatment
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Bone Metastasis in Cancer

I. Bone Metastasis in Breast Cancer

Bone Metastasis in Breast Cancer

- Bone is one of the earliest and most common sites of breast cancer metastasis. [Singletary, S. E(2003)]

- Between 30-85% of patients with metastatic breast cancer will develop bone metastases during the course of the disease. [Vassiliou, V (2013)]

- Median survival for bone only metastasis was 24-48 months. [Solomayer, E.(2000)]
  - As high as 72 months in one study [Briasoulis, E(2004)]
  - Median survival for Visceral metastasis was 12 months [Solomayer, E.(2000)]
  - 5-year Survival rate was 39% [Dürr, H. R(2002)]

The Nursing needs to focus on QI.
Incidence of Bone Metastasis

- Axial skeleton >> extremities
- Vertebrae > Pelvis > Ribs > Skull > Femur

Fig. 3. The distribution of skeletal metastases, as shown on the skeletal scintigram, in 50 patients with advanced mammary carcinoma.

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Bone remodeling process

Note: The osteoclast has a ruffled edge (bottom) that is attached to the bone and secretes acids and enzymes to dissolve the bone mineral and remove the collagen (connective tissue). This osteoclast is eating through a bone trabecula, part of the honeycombed structure of cancellous (spongy) bone.

Figure 2. Bone Resorption: An Osteoclast Destroying Bone
Note: Copyright 2009 by Hans-Ulrich Osterwalder/Photo Researchers, Inc. Used with permission.

II. Process

Source: Am J Health-Syst Pharm © 2006 American Society of Health-System Pharmacists
Process of Bone Metastasis

II. Process

“Vicious cycle” of Osteolytic Bone Metastasis

1. Tumour cells produce factors that stimulate osteoblasts to secrete RANKL
2. Osteoblasts and other bone cells increase expression of RANKL
3. Over-expression of RANKL drives increased formation, function and survival of osteoclasts, leading to excessive bone resorption
4. Bone resorption releases growth factors from the bone matrix that may perpetuate tumour activity

RANKL: Receptor Activator of Nuclear Factor Kappa B Ligand

# Type of Bone Metastasis

<table>
<thead>
<tr>
<th>Osteolytic metastasis</th>
<th>Osteoblastic metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breaking down old bone without making new bone → weaken the bones → easily break</td>
<td>Making new bone without breaking down old born → the bone harder (sclerosis) → easily break</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Breast cancer</th>
<th>Prostate cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detected on X-ray (after 3wks, except spine)</td>
<td>Not detected on X-ray → Bone scan</td>
</tr>
</tbody>
</table>
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Complication of Bone metastasis

- Pain
- SREs (Skeletal-Related Events)
  - Pathologic Fracture
  - Radiation Therapy
  - Surgical intervention
  - Spinal cord compression
  - Hypercalcemia
The hallmark symptom of bone metastasis

Character of bone pain on metastasis

- Dull aching pain
- Usually develops gradually
- Increasing at night
- Increasing in weight bearing

Pain assessment Parameters

- Physical
  - Onset - Acute, chronic, Breakthrough
  - Location
  - Duration
  - Type of pain - sharp, dull, etc.
  - Aggravating factors and Relieving factors
  - Treatment

- Psychological
  - History of anxiety, depression or other illness
  - Cognition
  - Usual coping strategies
  - Psychological responses

- Social
  - Interference of pain with activities of daily living
  - Family communication and response to illness and support system

- Spiritual
  - Presence of a spiritual community and belief
Pain management

III. Complication

- Diffused pain
  - Analgesics: WHO Pain Ladder
    - Adjuvant agent of Bone metastasis: Bisphosphonate, steroid, etc.
  - Radiopharmaceutical (Strontium-89 chloride: Metastron)

- Localized pain
  - External Beam Radiation Therapy
  - Nerve Block

Pain management

- Education
  - Reporting New or worsening signs and symptom (pain, neurologic change)
  - Keeping a Diary of pain score or other adverse event

- Emotional Support
  - Depression
  - Anxiety

SREs (Skeletal-Related Events)

- Pathologic Fracture
- Radiation Therapy to Bone
- Surgery to Bone
- Spinal Cord Compression
- Hypercalcemia

✓ Consequences
- SREs decrease patients’ functional independence and thus limit their autonomy
- SREs are associated with increases in
Pathologic Fracture

- 9-29% of patients with bone metastasis
- Fractures have been associated with decreased survival
- Symptom
  - Sudden Onset of sharp bone pain
  - Nerve involvement → Radiated pain
- Most frequent site: Long bone
- Intervention: Surgery
- Patient Education: High risk for injury
  - Call light in reach, Well-lit environment
  - Bed in a low position
  - Use of handrail while ambulating
  - Non-slip footwear
  - Removal throw rugs and cords from floor area

Spinal Cord Compression

- **Oncologic Emergency**
  - 5% of all patients with cancer
  - Early sign
    - Pain: local, radicular or both
    - Motor weakness or dysfunction, Sensory loss
  - Late sign
    - Loss of sensation for deep pressure, vibrations, posture
    - Incontinence or retention of urine or stool
    - Sexual impotence
    - Paralysis, Muscle atrophy
    - Loss of sweating below lesion
- Intervention: Steroid → Surgery ± Radiation Therapy
- Patient Education
  - Possibility of SCC, Early sign & Late sign

### Hypercalcemia

- **Oncologic Emergency**
  - 5% of all patients with cancer
  - 80% Parathyroid hormone released protein produced by solid tumor
  - 20% Local Osteolytic hypercalcemia

<table>
<thead>
<tr>
<th>Serum Total Calcium Range</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Anorexia, Lethargy, Urinary frequency,</td>
</tr>
<tr>
<td></td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>10.5 - 11.5mg/dL</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Constipation, Weakness, Dehydration,</td>
</tr>
<tr>
<td>11.5 - 13.5mg/dL</td>
<td>Arrhythmia</td>
</tr>
<tr>
<td>Severe</td>
<td>Ileus, Seizure, Renal failure, Arrest</td>
</tr>
<tr>
<td>&gt;13.5mg/dL</td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>Massive N/S hydration &amp; loop diuretic</td>
</tr>
<tr>
<td></td>
<td>Bisphosphonate or Denosumab</td>
</tr>
</tbody>
</table>

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Skeletal Scintigraphy (Bone scan)

X-ray

CT (Computed Tomography)

MRI (Magnetic Resonance Imaging)

PET (Positron Emission Tomography)

**Purpose**
- Diagnosis
- Check the response of treatment

**Optimal imaging Modality**
Skeletal Scintigraphy (Bone scan)

- Most common modality for Detecting bone metastasis
- Uses of Radiopharmaceuticals reflects bone metabolism
- Appearance ; Hot spot
- Sensitivity ; Varies (62-100%)
- Advantage ; Produce Whole body image at a reasonable cost
- Disadvantage ; Low specificity, “Flare” phenomenon
- Preferred Sites ; Appendicular bone

Active bone lesion in the sternum, L1, L4, sacrum, multiple bony metastases.
X-ray

- Appearance
  - Osteolytic lesion; Faint or Absent density
  - Osteoblastic lesion; Sclerotic lesions or rims
- Sensitivity; Low (44-50%)
- Advantage
  - Demonstrates structural changes
  - Assesses risk of pathologic fracture
  - No need for contrast injection
  - Less expensive
- Disadvantage
  - Delayed appearance of response

Suspicious osteoblastic lesion, L1 - r/o bone metastasis
CT (Computed Tomography)

- **Appearance**
  - Lytic, sclerotic, mixed for bone, Higher attenuation for marrow
- **Sensitivity** ; High (71-100%)
- **Advantage**
  - Higher specificity than Bone scan
  - Evaluates cortical and cancerous bone and calcifications more accurately
- **Disadvantage**
  - Local images
- **Preferred Sites** ; Axial skeleton
MRI (Magnetic Resonance Imaging)

- Appearance: Lower or higher intensity
- Sensitivity: High (82-100%)
- Advantage
  - Higher specificity than Bone scan and X-ray
  - Evaluates spinal cord compression and soft tissue more accurately than CT
  - No ionizing radiation
- Disadvantage
  - Poor cortical bone detail
  - Expensive
PET (Positron Emission Tomography)

- Appearance: Hot spot
- Sensitivity: Varies (62-100%)
- Advantage: Detects new marrow lesions
- Disadvantage
  - Not specific to bone
  - False-positives after G-CSF
  - Very Expensive
- Preferred Sites: Bone marrow

Newly HM bone lesions in L1, L4, sacrum
HM bone lesion in sternum.
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Treatment in Bone Metastasis

1) Endocrine Therapy
2) Chemotherapy
3) Radiation therapy
4) Surgical Intervention
5) Bone modifying agent
## V. Treatment

### Endocrine Therapy & Chemotherapy

<table>
<thead>
<tr>
<th>Endocrine Therapy &amp; Chemotherapy</th>
<th>근거수준</th>
<th>참고문헌</th>
</tr>
</thead>
<tbody>
<tr>
<td>전신전이 내분비요법</td>
<td>2</td>
<td>36</td>
</tr>
<tr>
<td>내분비요법으로 사용되는 약제는 tamoxifen, 아로마타제억제제, fulvestrant가 대표적이고 세 번의 서로 다른 약제를 시도한 후에도 병이 진행하거나 반응이 없는 경우에는 항암 화학요법이나 표적치료를 고려하는 것이 바람직하다.</td>
<td>1</td>
<td>36-55</td>
</tr>
</tbody>
</table>

✔️ Compliance of treatment
Radiation therapy

- **Purpose**
  - Pain relief (the Best method: response rate 80-90%)
  - Local control

- **Dose**
  - 30Gy in 10 fraction
  - 8Gy in 1 fraction

- **Side effect**
  - Fatigue
  - Nausea, anorexia
  - Skin irradiation
  - Low blood count
  - Diarrhea (in case of pelvic area radiation)
Surgical Intervention

- Purpose
  - Prevent pathologic fracture
  - Treat an actual fracture
  - Stabilize the spine
Bone modifying agent

Indication

<table>
<thead>
<tr>
<th>Indication</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates or denosumab</td>
<td>Add denosumab, zoledronic acid, or pamidronate</td>
</tr>
</tbody>
</table>

**V. Treatment**

**NCCN Guidelines Version 1.2017**
Invasive Breast Cancer

**TREATMENT OF STAGE IV DISEASE**

- **Bone disease present**
  - Add denosumab, zoledronic acid, or pamidronate
- **Bone disease not present**
Bone modifying agent

- **Bisphosphonate**
  - Pamidronate 90mg IV over 2 hours q 3-4 weeks
  - Zoledronic acid 4mg IV over 15 minutes q 3-4 weeks

- **Denosumab 120mg SC q 4 weeks**

  ✓ Dose adjustment for saving renal function
  → Adherence to dosing time and interval
건강보험심사평가원의 급여기준

V. Treatment

IV. 기타약재

<table>
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<tr>
<td>- filgrastim(품명: 고라신 주)</td>
</tr>
<tr>
<td>- lenograstim(품명: 레트로간주)</td>
</tr>
<tr>
<td>- pegfilgrastim(품명: 울타스티포락트다케민주)</td>
</tr>
<tr>
<td>- peglotocin(품명: 런릭락리피랄도락난주)</td>
</tr>
<tr>
<td>- trabecilast(품명: 트레아스탄주사액저알동도시간)</td>
</tr>
<tr>
<td>- sarglocase(품명: 후즈스프리클도주)</td>
</tr>
<tr>
<td>2. Zoledron acid 주사제(품명: 조메타론 주) ............ 150</td>
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<td>3. Sodium thiosulfate 주사제(품명: 이메독스주 25%) ... 165</td>
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<tr>
<td>4. Doxorubicin 주사제(품명: 가다옥신주) .................. 186</td>
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</tbody>
</table>
건강보험심사평가원의 급여기준

가. 악성종양으로 인한 과칼슘혈증: albumin-corrected calcium 13mg/dl 이상인 경우에 1차적으로 투여 시 인정하고, 12mg/dl 이상 13mg/dl 미만인 경우에는 1차적으로 pamidronate 제제 투여 후 재차 투여하는 경우에 한하여 인정
나. 다발골수종의 골병변 또는 유방암, 전립선암의 골전이에 표준항암요법과 연계하여 투여 시 다음과 같이 인정함

- 다음 -

(1) 투여조건
단순 방사선 검사(plain X-ray)상 lytic 소견을 보이는 경우, 또는 X-ray 상 정상이나 CT 또는 MRI로 골파괴가 명확히 입증된 경우에 인정함. 단, bone scan만으로 이상 소견이 확인된 경우는 인정하지 아니함

(2) 표준항암요법의 범위 및 연계투여의 범주
항암제 또는 호르몬제 치료가 해당되며, 항암제 또는 호르몬제를 치료 중인 경우에 인정하되, 최근 4주 이내에 적절한 항암제 또는 호르몬제가 투여된 경우에 인정함(항암제 치료 cycle 중 휴약기간 등은 사례별 적용)
- 다만, 호르몬 수치 조절 목적으로 수술(전립선암의 경우 고환적출술, 유방암의 경우 난소적출술)을 실시한 경우에는 호르몬제 치료로 간주함
- 항암제 및 호르몬제 치료에 실패한 환자에서 weight-bearing bone의 전이 등으로 방사선치료를 시행하는 경우 zoledronic acid 주사제 사용을 인정함
건강보험심사평가원의 급여기준

(3) 암종별 적용기준
○ 전립선암: 허가사항(최소 1회 이상 호르몬 치료 후 병이 진전된 경우에 사용) 범위 내에서 필요·적절하게 투여 시 인정함
○ 유방암: 허가사항 범위 내에서 필요·적절하게 투여 시 인정함
○ 다발골수종: pamidronate 제제 사용 후 반응이 없는 경우에 한하여 인정함

(4) 투여중지 기준
동 약제 투여기간 중 매 3개월마다 단순 방사선 검사(plain X-ray) 등으로 골병변 또는 골전이에 대한 평가를 실시하여 새로운 골관련 합병증(SRE, skeletal-related events)이 발생한 경우에는 투약을 중단토록 하되, 중지의 기준이 되는 SRE의 범주는 다음과 같음
- Pathologic fracture(병적 골절)
- Surgery to bone(뼈 수술)
- Hypercalcemia of malignancy(새로 발생한 고칼슘혈증)

※ 허가사항 범위이지만 상기 인정기준 이외에 투여하는 경우의 비용부담은 보건복지부 고시
【개정 제2016-263호:2016.12.28】에 따라 약값 전액을 본인이 부담토록 함
Bone modifying agent – Bisphosphonate

- Mechanism
  - Inhibition of osteoclast activity
  - Promote osteoclast apoptosis
  - Slow down the action of osteoclast

http://www.nature.com
Bone modifying agent – Bisphosphonate

- Relative Potency

Table 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generation</th>
<th>Relative Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etidronate</td>
<td>First</td>
<td>1</td>
</tr>
<tr>
<td>Clodronate</td>
<td>First</td>
<td>10</td>
</tr>
<tr>
<td>Tiludronate</td>
<td>Second</td>
<td>10</td>
</tr>
<tr>
<td>Alendronate</td>
<td>Second</td>
<td>100</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>Third</td>
<td>100–1,000</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Third</td>
<td>1,000–10,000</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>Third</td>
<td>1,000–10,000</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>Third</td>
<td>10,000+</td>
</tr>
</tbody>
</table>

Bone modifying agent – Denosumab

- Fully human monoclonal antibody against RANKL
- Action

Bone modifying agent

Effect

- Reducing bone pain
- Slowing down bone damage caused by the cancer
- Lowering the risk of broken bones
- Reducing high blood calcium levels

✓ Improved Quality of life & Overall survival

Monczewski, L. (2013)
Bone modifying agent

- Side effect
  - Acute-phase reaction (Denosumab < Bisphosphonate)
    - Including Flu-like symptom and increasing bone pain
    - During the first 3 days following initial therapy & Self limiting
    - Relief by NSAIDs and Antipyretics (Acetaminophen)
  - Renal toxicity: serum creatinine level check (Creatinine Clearance >60mL/min)
  - Hypocalcemia (Denosumab > Bisphosphonate)
    - Incidence: 5%
    - With Vitamin D, Calcium
    - Creatinine clearance <30mL/min or on dialysis → close monitoring for hypocalcemia

- ONJ Osteonecrosis of the jaw (Denosumab > Bisphosphonate)

ONJ (Osteonecrosis of the jaw)

- Uncommon but potentially serious condition (Incidence 5.48%)
- Definition
  - An area of exposed bone in the maxillofacial or mandibular region that does not heal within 8 weeks after identification by a health care provider
  - Patient who was receiving or had been exposed to a bisphosphonate administered orally or IV
  - Patient who had not had radiation therapy to the craniofacial region

V. Treatment
ONJ (Osteonecrosis of the jaw)

- Risk factor
  - IV bisphosphonate (zoledronic acid)
  - Duration exposure (longer)
  - Cumulative dose of drug
  - Inflammatory condition
  - Osteomyelitis of the jaw
  - Invasive dental procedure

- Education
  - Dental examination with preventive dentistry prior to initiation of bisphosphonate therapy
  - Maintain optimal oral hygiene
    - Including brushing and flossing after meals and use of a fluoride mouth rinse
  - Avoid invasive dental procedures that involve mandible bone or periotenon.
Summary

- Bone is the most common site of breast cancer.
- The survival of bone metastasis in breast cancer is relatively long.
- The complications of bone metastasis are Pain, Pathologic fracture, Radiation therapy, Surgical intervention, Spinal cord compression and Hypercalcemia.
- Treatments are Endocrine Tx, CTx, RTx, OP and the Bone modifying agents.
- Adverse events of the bone modifying agents are acute phase reaction, renal toxicity, hypocalcemia and osteonecrosis of the jaw.
Take Home message

- Skillful Assessment
- Prompt recognition of complication & prevent complications
- Knowledge of the treatment plan
- Implementing interventions & promote positive outcomes
- Emotional support of Psychosocial distress (especially depression and anxiety)

✓ The nurse will help patients throughout their cancer journey and maintain the highest quality of life.
Thank you for your listening