Current **strategies** to maintain bone health, and emerging bone health issues in cancer patients

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Disclosures

- none
Aims

- To develop an understanding of the management of bone metastasis through a multidisciplinary approach
- Enable the learner to understand the guidelines of management of bone complications and the use of bisphosphonates and denosumab
- Describe the challenges in management of bone metastasis
About bone metastases

- One of the most common places for prostate or breast cancer to spread is to the bone
  - Approximately 65 to 75 per cent of people with advanced prostate or breast cancer experience bone metastases

- Growing cancer cells weaken and destroy bone around the tumour

- Can lead to debilitating complications
Bone metastasis

- most prevalent in advanced breast (70–80%), prostate (70–80%), thyroid (60%), lung (10–50%) and renal cancers (30%)

- The consequences of bone metastases include reduced survival, morbidity and pain that negatively affect the patient's quality of life (QoL) as well as skeletal–related events (SREs)
Signs

- Asymptomatic
- Bone pain
- Fracture
- hypercalcemia
Skeletal Related Events (SREs) in Cancer Have Potentially Severe Consequences

Pain
50-90% of patients with bone metastases

Pathologic fracture
Radiotherapy to bone
Spinal cord compression
Surgery to bone

22% 29% 7% 3%  

External beam radiotherapy (EBRT) continues to be the mainstay for the treatment of pain and/or prevention of morbidity caused by bone metastases.

The evidence for the safety and efficacy of re-treatment to previously irradiated areas of peripheral bone metastases pain is derived from both prospective studies and retrospective data, and it has been shown to be safe and effective.
Guideline statement

• Multiple prospective randomized trials have shown pain relief equivalency for dosing schema including 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, and a single 8 Gy fraction for patients with previously un-irradiated painful bone metastases.

• Fractionated treatment courses are associated with an 8% re-treatment to the same anatomic site due to recurrent pain versus 20% after a single fraction, while the single fraction treatment approach optimizes patient and caregiver convenience.
Efficacy of single dose radiation

• All of the completed studies for either a single 8 Gy fraction or multiple fractions have confirmed similar rates of pain relief varying from 50%-85% for peripheral and vertebral bone metastases.

Stereotactic radiation

The use of stereotactic body radiotherapy was seen to hold theoretical promise in the treatment of new or recurrent spine lesions, though the Task Force recommended that its use be limited to selected patients preferably treated on a prospective trial.
Surgical decompression and post-operative radiotherapy is recommended for spinal cord compression or spinal instability in highly selected patients with sufficient performance status and life expectancy.

The use of bisphosphonates, radionuclides, vertebroplasty and kyphoplasty for the treatment or prevention of cancer related symptoms does not obviate the need for EBRT in appropriate patients.
Mechanism

Range of beta particle

Range of alpha particle

Tumor

Bone marrow

Bone

Bone-surface

Alpha particles: localised cell killing with minimal non-target toxicity
Most recently, this has been evident in studies examining the radiopharmaceutical radium–223 dichloride (Xofigo) in patients with mCRPC.

The ALSYMPCA trial, which was the basis for the 2013 FDA approval of radium–223, showed a median overall survival (OS) of 14 months with radium–223 versus 11.2 months with placebo (HR, 0.70; \( P = .00185 \)) in patients.
Survival

Probability of survival vs. Time (Weeks)

- Alpharadin
- Placebo

Maximum treatment duration

HR 2.103, p = 0.017
ASCO/Cancer Care Ontario- Breast Adjuvant Guidelines

• "It is recommended that, if available, zoledronic acid (4 mg intravenously [over 15 minutes or longer] every 6 months [for 3 to 5 years]) or clodronate (1,600 mg/d orally [for 2 to 3 years]) be considered as adjuvant therapy for postmenopausal patients with breast cancer who are deemed candidates for adjuvant systemic therapy

Dhesy-Thind S, Flechther GG, Blanchette S et al. Use of Bisphosphonates and other disease modifying agents in breast cancer JCO 2017 ;35:18 2062-2081
Breast Cancer Guidelines

1. Postmenopausal women in the decade after beginning treatment, 5 years of AI therapy reduces the risk of dying from breast cancer by around 40%, compared with no endocrine therapy (and reduces the risk for breast cancer mortality by about 15% compared with tamoxifen).

2. 2 to 5 years of bisphosphononates adjuvant, reduces the risk of dying from breast cancer by 18%

Early Breast Cancer Trialist Collaborative Group 2017
Bisphosphonates reduce the risk of SREs in breast cancer patients

- **Zoledronate 4 mg**
  - Kohno 2005
  - Risk reduction: 41%
  - P value: 0.001

- **Pamidronate 90 mg**
  - Aredia study 18 and 19
  - Risk reduction: 23%
  - P value: <0.001

- **Ibandronate 6 mg**
  - Body 2003
  - Risk reduction: 18%
  - P value: 0.04

- **Ibandronate 50 mg**
  - Body 2004
  - Risk reduction: 14%
  - P value: 0.08

- **Oral clodronate 1,600 mg**
  - Kristensen 1999
  - Paterson 1993
  - Tubiana-Hulin 2001
  - Risk reduction: 31%
  - P value: 0.03 (pooled)

Cochrane database comparing placebo-controlled trials in breast cancer setting.

Adapted from Pavlakis N, et al. Cochrane Database Syst Rev 2005;CDC003474
Study Schema

Patients aged ≥18 years with:
- Histologically or cytologically confirmed breast adenocarcinoma
- Evidence of 1 or more bone metastases
- Adequate organ function
- ECOG performance status of 0, 1, or 2

120 mg denosumab SC and IV placebo every 4 weeks

RANDOMIZATION

ZA 4 mg IV and SC placebo every 4 weeks

Primary end point
- Time to first on-study SRE (non-inferiority test)

Secondary end points
- Time to first on-study SRE (superiority)
- Time to first and subsequent on-study SRE (superiority)

BSAP = Bone-specific alkaline phosphatase
ECOG = Eastern Cooperative Oncology Group
SC = Subcutaneous

Primary End Point: Time to First On-Study SRE

Improved efficacy with denosumab was observed as early as six months

HR = 0.82 (95% CI, 0.71-0.95) *
p < 0.001 (non-inferiority)
p = 0.01 (superiority)

- IV ZA 4 mg every 4 weeks (n = 1020)
- SC denosumab 120 mg every 4 weeks (n = 1026)

* Adjusted for multiplicity

Study Month

No. at risk
IV ZA 1020 829 676 584 498 427 296 191 94 29
SC denosumab 1026 839 697 602 514 437 306 189 99 26

CI = Confidence interval; HR = Hazard ratio.

ZOOM: A Prospective, Randomized Trial of ZA for Long-Term Treatment of Bone-metastatic BrCa after 1 Year of ZA Treatment

N = 420 (Planned)
Key eligibility criteria
• BC Stage IV
• Confirmed bone metastasis
• Prior zolendronic acid treatment (4mg q4 wk) = 9-12 infusions

R 1:1

Arm 1: Zolendronic acid (4mg q 12 wk)
Arm 2: Zolendronic acid (4mg q 4 wk)

Treatment duration 1 year

Endpoints:
Primary: Skeletal morbidity rate (SMR)
Secondary: Proportion of patients experiencing SREs (overall and by event), time to first SRE, SMR by event, bone pain, use of analgesics, bone marker levels, safety

Accrual: February 2006 – February 2010
### ZOOM: Primary Efficacy Analysis: SMR

<table>
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<tr>
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<th>ZOL q 12 wk (Arm 1)</th>
<th>ZOL q 4 wk (Arm 2)</th>
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<tbody>
<tr>
<td>N (ITT population)</td>
<td>209</td>
<td>216</td>
</tr>
<tr>
<td>Mean SMR (95% CI)</td>
<td>0.26 (0.15, 0.37)</td>
<td>0.22 (0.14, 0.29)</td>
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<tr>
<td>95% CI</td>
<td>-0.09 to 0.17</td>
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The upper limit of the CI (0.17) was less than the recalculated non-inferiority margin of 0.19. This result indicates that the efficacy of the q 12 wk arm was not inferior to the q 4 wk arm.

Three Identically Designed Head-to-Head Studies Comparing Denosumab vs Zoledronic Acid

- **Breast Cancer**
  - (n = 2046)
- **Prostate Cancer**
  - (n = 1901)
- **Other Solid Tumors or Multiple Myeloma**
  - (n = 1776)

**Randomization**

- **Denosumab 120 mg SC** and placebo IV every 4 weeks
- **Zoledronic acid 4 mg IV** and placebo SC every 4 weeks

**Integrated Analysis Prespecified**

- (n = 5723)

Daily supplementation of calcium ≥ 500 mg and vitamin D ≥ 400 IU were recommended in both arms of the study.
First and Subsequent SRE

Prostate Cancer Study\textsuperscript{1, 4} (N = 1901)

Total SREs:
- Denosumab\textsuperscript{TM}: 494
- Zoledronic acid: 584

18% Risk Reduction
Questions and Challenges

Basic Science

Are osteoclasts the only stromal cell type that should be targeted therapeutically?

Are there new cancer/bone–stromal targets that should be developed?

What is our understanding of the biological mechanisms of pain associated with bone metastasis?

Clinical

What are the major issues affecting cancer patients with bone metastasis?

What do patients, nurses and clinicians feel are the most immediate concerns (bone pain, mobility issues, and survival)?

Why do bisphosphonates and denosumab for metastatic bone cancers fail to prolong overall survival?
Experimentally, the most frequent route of injection of cancer cells is intracardiac (into left cardiac ventricle), which permits seeding and colonization of tumor cells in metaphyses of the long bones.

Intratibial (intraosseous) injection of tumour cells directly into the marrow space is often used to examine tumour stromal interactions during the growth of bone metastatic lesions.

Optical imaging systems (IVIS), radiography, μCT and MRI) have been used to assess the growth of bone metastatic lesions and the effect on bone resorption/destruction.
Mechanism of bone metastasis

- isolate new bone metastatic-derived cancer cell lines, to test drug combinations in ex vivo bone metastatic tumour tissues and to develop patient derived xenograft models. There remain challenges in translating these models into the clinical practice, such as a need to improve quantitative assays for tumour burden and ultimately evaluate response to treatment in vivo and models that can better mimic to the human in vivo phenotype.
Cabozantinib (XL184) is an orally bioavailable tyrosine kinase inhibitor with potent activity against MET and VEGFR2. In early clinical studies in patients with metastatic prostate cancer, cabozantinib demonstrated significant and rapid effects on bone scan lesions as well as on markers of bone formation and resorption, bone pain and narcotic use. In addition, statistically significant improvement in progression-free survival was seen with cabozantinib compared with placebo. While the subsequent larger registration study was negative in terms of overall survival
Cabozantinib

- Inhibitor of MET and VEGFR-2
- Phase II results
- 76% showed bone metastasis shrinking
- 108 patients, 21 demonstrated complete resolution of bone lesions and 61 had partial shrinkage

Choueri T et al 2018
Radium 223

- Radium 223 and pembrolizumab
- Prepare the microenvironment
- Principles and challenges
Apalutamide

- First drug in prostate cancer to prevent metastasis
Thank You

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