MASCC/IS00 2019
ANNUAL MEETING · SAN FRANCISCO

21-23 JUNE 2019
Supportive Care Makes Excellent Cancer Care Possible #MASCC19
Epidemiology of Bone Health Issues in Patients With Cancer
Invited Speaker: Beatrice Edwards, USA

14:05 - 14:25

Functional and Psychosocial Consequences of Fractures
Invited Speaker: Nelson Watts, USA

14:25 - 14:45

Clinical Guidelines for the Management of Bone Health in Patients With Cancer
Invited Speaker: Matti Aapro, Switzerland

14:45 - 14:55

EFFECT OF FRACTURES ON OVERALL SURVIVAL IN CANCER PATIENTS: THE NHANES DATABASE
Speaker: B. Edwards, USA

14:55 - 15:05

PAIN FLARE-EFFECT PROPHYLAXIS WITH CORTICOSTEROIDS ON BONE RADIOOTHERAPY TREATMENT: A SYSTEMATIC REVIEW
Speaker: C. Fabregat Franco, Spain
Clinical Guidelines for the Management of Bone Health in Patients With Cancer

Matti S. Aapro
Cancer Center
Genolier
Switzerland
COI

Dr Aapro is/was a consultant for Accord, Amgen, BMS, Celgene, Clinigen, Eisai, Genomic Health, G1, GSK, Helsinn, Hospira, JnJ, Novartis, Merck, Merck Serono, Pfizer, Pierre Fabre, Roche, Sandoz, Tesaro, Teva, Vifor

and has received honoraria for lectures at symposia of Accord, Amgen, Angelini, Bayer Schering, Biocon, Cephalon, Chugai, DRL, Eisai, Genomic Health, Glenmark, GSK, Helsinn, Hospira, Ipsen, JnJ OrthoBiotech, Kyowa Hakko Kirin, Merck, Merck Serono, Mundipharma, Novartis, Ono Pharmaceuticals, Pfizer, Pierre Fabre, Roche, Sandoz, Sanofi, Tesaro, Taiho, Teva, Vifor

No responsibility accepted for involuntary errors or omissions. The list may be incomplete, and does not reflect consultancy for NGOs, Universities, Governmental agencies, and others.
WHOM TO THANK?

Laura Biganzoli
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Ingo Diel
Michael Gnant
Peyman Hadji
Juan Morote
Trevor Powles
Tiina Saarto
And many others
General and Supportive Care

Bone health in the elderly cancer patient: a SIOG Position Paper

J.J. Body, E. Terpos, B. Tombal, P. Hadji, A. Arif, A. Young, M. Aapro, R. Coleman

PII: S0305-7372(16)30104-9
DOI: http://dx.doi.org/10.1016/j.ctrv.2016.10.004
Reference: YCTRV 1560

To appear in: Cancer Treatment Reviews Cancer Treatment Reviews

Received Date: 17 October 2016
Accepted Date: 19 October 2016

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The menu

- Which guidelines, why?
- Messages from guidelines
- To conclude
The menu

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- Messages from guidelines
- To conclude
A HUGE THANKS TO

Jim Koeller, MS

Professor of Medicine, Oncology & Pharmacy
University of Texas at Austin & the Health Science Center, San Antonio
Goals of Guidelines

- To provide a framework and thought process for specific patient management
  - Should result in decreased variation
- Evaluate available evidence (establishing the quality and degree of concurrence by expert reviewers) and provide recommendations based of it
- Can provide expert ‘opinion’ when evidence is missing (based on guideline intent)
CRITERIA FOR TRUSTWORTHY GUIDELINES

The Institute of Medicine (IOM) Report 2011

According to the Institute of Medicine’s clinical practice guidelines report, trustworthy guidelines should:
- Be based on a systematic review of the existing evidence
- Be developed by a knowledgeable, multidisciplinary panel of experts and representatives from key affected groups
- Consider important patient subgroups and patient preferences, as appropriate
- Be based on an explicit and transparent process that minimizes distortions, biases, and conflicts of interest
- Provide a clear explanation of the logical relationships between alternative care options and health outcomes, and provide ratings of both the quality of evidence and the strength of recommendations
- Be reconsidered and revised as appropriate when important new evidence warrants modifications of recommendations

Reference: Committee on Standards for Developing Trustworthy Clinical Practice Guidelines: Clinical Practice Guidelines We Can Trust. Washington, DC; Institute of Medicine, 2011.

Proliferation Of GUIDELINES
- Approaches to Guidelines Development -

• Evidence-based (expert panel)
  – ESMO; MASCC; ASCO (international relevance)

• Consensus-based (opinion-expert panel)
  – NCCN (should be only US but…)

• Economically-based
The menu

- Which guidelines, why?

- Messages from guidelines

- To conclude
BONE...
CANCER and ITS TREATMENT

LET US NOT FORGET
THE BACKGROUND
Lifetime of osteoporosis related skeletal events:

<table>
<thead>
<tr>
<th>Event</th>
<th>Women (%)</th>
<th>Men (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporotic fracture</td>
<td>46-53</td>
<td>21-22</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>15-23</td>
<td>5-11</td>
</tr>
<tr>
<td>Radiographic vertebral fracture</td>
<td>27%</td>
<td>11%</td>
</tr>
<tr>
<td>Clinical vertebral fracture</td>
<td>15%</td>
<td>8%</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>10-13</td>
<td></td>
</tr>
<tr>
<td>Prostate cancer</td>
<td></td>
<td>9-11%</td>
</tr>
</tbody>
</table>

NB: variable between countries

As trabecular and cortical bone loss progresses, vertebral and hip fracture rates increase exponentially.

Adapted from: Sambrook P & Cooper C. *Lancet* 2006;367:2010–2018

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**Graph:**

- **Vertebral fractures**
- **Hip fractures**

**Legend:**

- Early increased incidence of vertebral fracture correlating with early trabecular bone loss
- Later increased incidence of hip fracture correlating with accumulation of trabecular and cortical bone loss

**Table:**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Incidence per 10,000 women per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>50−54</td>
<td>0</td>
</tr>
<tr>
<td>55−59</td>
<td>0</td>
</tr>
<tr>
<td>60−64</td>
<td>0</td>
</tr>
<tr>
<td>65−69</td>
<td>0</td>
</tr>
<tr>
<td>70−74</td>
<td>0</td>
</tr>
<tr>
<td>75−79</td>
<td>0</td>
</tr>
<tr>
<td>80−84</td>
<td>0</td>
</tr>
<tr>
<td>85+</td>
<td>0</td>
</tr>
</tbody>
</table>

Adapted from: Sambrook P & Cooper C. *Lancet* 2006;367:2010–2018
Risk of fracture after androgen deprivation for prostate cancer


- No androgen deprivation (n = 32,931)
- GnRH agonist, 1-4 doses (n=3763)
- GnRH agonist, 5-8 doses (n=2171)
- GnRH agonist, ≥ 9 doses (n=5061)
- Orchiectomy (n=3399)
Limitations:

- Literature rather than individual patient data meta-analysis
- Reports of trials with different durations of follow-up
- Information on the potentially confounding baseline host factors (e.g., obesity, hypertension, diabetes, and family history of events of interest) or the use of concurrent medications was not reported
Summary of Recommendations

Recommendations Unchanged From 2011 Guideline Update

• BMAs are recommended for patients with metastatic breast cancer with evidence of bone destruction.

• One BMA is not recommended over another.

• Mechanism of action, as well as the potential benefits and harms, should be taken into account when considering long-term use of BMA.

• In patients with creatinine clearance > 60 mL/min, no change in dosage, infusion time, or interval is required; monitor creatinine level with each intravenous bisphosphonate dose.

• In patients with creatinine clearance < 30 mL/min or on dialysis who may be treated with denosumab, close monitoring for hypocalcemia is recommended.

• All patients should have a dental examination and preventive dentistry before using a BMA.

• Use of biochemical markers to monitor BMA use is not recommended for routine care.
clinical practice guidelines

Bone health in cancer patients: ESMO Clinical Practice Guidelines†

R. Coleman¹, J. J. Body², M. Aapro³, P. Hadji⁴ & J. Herrstedt⁵ on behalf of the ESMO Guidelines Working Group*

¹Weston Park Hospital, Cancer Research-UK/Yorkshire Cancer Research Sheffield Cancer Research Centre, Sheffield, UK; ²CHU Brugmann, Université Libre de Bruxelles, Brussels, Belgium; ³Multidisciplinary Oncology Institute, Genolier, Switzerland; ⁴Department of Gynecology, Endocrinology and Oncology, Philipps-University of Marburg, Marburg, Germany; ⁵Department of Oncology, Odense University Hospital, Odense, Denmark
ESMO clinical practice guideline: Bone health in cancer patients

• Clinicians treating cancer patients need to be aware of:
  • Treatments to reduce skeletal morbidity in metastatic disease
  • Strategies to minimise cancer treatment-induced skeletal damage

• ESMO guidelines “provide a framework for maintaining bone health in patients with cancer”
## Diagnosis: Recommended techniques

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isotope bone scan</strong></td>
<td>• Sensitive test used to detect presence of skeletal pathology</td>
</tr>
<tr>
<td></td>
<td>• Gives little information about nature of damage/metastatic disease</td>
</tr>
<tr>
<td><strong>CT and MRI</strong></td>
<td>• Recommended for obtaining structural information on skeletal damage from metastatic bone disease</td>
</tr>
<tr>
<td><strong>PET</strong></td>
<td>• Provides functional information that may aid in diagnosis</td>
</tr>
<tr>
<td><strong>DXA scan</strong></td>
<td>• Recommended for patients at risk of fracture or cancer treatment-induced bone loss</td>
</tr>
<tr>
<td><strong>Plain radiographs</strong></td>
<td>• <em>An insensitive test for metastasis – lesions need to be &gt;1cm with bone mineral loss of ~50% to be recognized</em></td>
</tr>
</tbody>
</table>
 COMMENTS

**Isotopic bone scanning**

- Not useful for monitoring treatment response

**Biochemical markers**

- e.g. amino (N) and carboxy (C) cross-linked telopeptides of type I collagen (NTC, CTX)
- May provide information on prognosis and response to treatments but are not recommended for routine clinical use
ESMO – 2014 Algorithm for managing Bone Health during Breast Cancer Treatment

Patient with cancer receiving chronic endocrine treatment known to accelerate bone loss

T-score > -2.0 and no additional risk factors
- Exercise
- Calcium and vitamin D
- Monitor risk and BMD at 1–2 year intervals

Any 2 of the following RF:
- Age >65 years
- T-score < -1.5
- Smoking (current or history)
- BMI < 20
- Family history of hip fracture
- Personal history of fragility fracture >50 years
- Oral glucocorticoid use for > 6 months

T-score < -2.0
- Exercise
- Calcium and vitamin D
- Bisphosphonate therapy (zoledronic acid, alendronate, risedronate, ibandronate) and Denosumab*
- Monitor BMD every 2 years
- Check compliance with oral therapy

*in view of ABCSG-18 data

Guideline for Bisphosphonates as Adjuvant: St Gallen/Vienna 2019 (notes taken by Aapro)

Is bisphosphonate treatment, such as zoledronic acid q 6 months or oral clodronate, during adjuvant endocrine therapy indicated to improve DFS irrespective of BMD?

• In postmenopausal patients?  YES 83.7%

Should adjuvant denosumab (60 mg twice a year) substitute for bisphosphonate?  NO 75%
Primary End Point Results

<table>
<thead>
<tr>
<th>Number of Fractures / Patients</th>
<th>Hazard ratio vs Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo 176 / 1,709</td>
<td>0.50 (0.39 - 0.65)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Denosumab 92 / 1,711</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients at risk:
Placebo: 1709, 1660, 1470, 1265, 1069, 921, 785, 637, 513, 384, 275, 185, 112
Denosumab: 1711, 1665, 1488, 1297, 1118, 965, 823, 688, 549, 432, 305, 221, 116
Effects Of Bisphosphonate Treatment On Recurrence And Cause-specific Mortality In Women With Early Breast Cancer: A Meta-analysis Of Individual Patient Data From Randomised Trials


Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)’s Bisphosphonate Working Group.

Published in Lancet Oncology 2014
Adjuvant bisphosphonates reduce the rate of bone metastasis and improve breast cancer survival in post-menopausal patients

EBCTCG Lancet 2014
Adjuvant AIs reduce the relapse rate and improve breast cancer survival in post-menopausal patients compared to tamoxifen.

**EBCTCG Lancet 2015**
A NICE REVIEW

https://doi.org/10.1007/s12609-018-0295-6

SYSTEMIC THERAPIES (M LIU AND T HADDA, SECTION EDITORS)

Bone-Modifying Agents in Early-Stage and Advanced Breast Cancer

Arielle Heeke¹ • Maria Raquel Nunes² • Filipa Lynce³,⁴
WHAT DOSE OF BP\textsubscript{s} TO USE in M1 BrCA

SEVERAL STUDIES INDICATE THAT MONTHLY Zoledronic ACID MAY NOT BE NEEDED FOR LONG-TERM CONTROL OF SREs

HOWEVER EXPERT CONSENSUS MIGHT SUGGEST MONTHLY FOR 3-6 MONTHS before 3 monthly

Amadori Lancet 2014; Hortobagyi ASCO 2014; Himelstein ASCO 2015
<table>
<thead>
<tr>
<th>Condition</th>
<th>Q Month N = 911</th>
<th>Q 3 Months N = 911</th>
<th>HR (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ZA dose (median)</td>
<td>56 mg</td>
<td>24 mg</td>
<td>— ( &lt; 0.01)</td>
</tr>
<tr>
<td>Dose delays</td>
<td>62%</td>
<td>37%</td>
<td>— ( &lt; 0.01)</td>
</tr>
<tr>
<td>Any SRE</td>
<td>260</td>
<td>253</td>
<td>1.05 (0.60)</td>
</tr>
<tr>
<td>Any SRE – breast pts (N = 820)</td>
<td>113</td>
<td>119</td>
<td>0.90 (0.43)</td>
</tr>
<tr>
<td>Any SRE – prostate pts (N = 660)</td>
<td>107</td>
<td>101</td>
<td>1.15 (0.31)</td>
</tr>
<tr>
<td>Any SRE – myeloma pts (N = 265)</td>
<td>35</td>
<td>30</td>
<td>1.30 (0.29)</td>
</tr>
<tr>
<td>Bone RT</td>
<td>185</td>
<td>163</td>
<td>1.16 (0.18)</td>
</tr>
<tr>
<td>Bone fractures</td>
<td>62</td>
<td>79</td>
<td>0.78 (0.13)</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>23</td>
<td>30</td>
<td>0.75 (0.30)</td>
</tr>
<tr>
<td>Bone surgery</td>
<td>22</td>
<td>42</td>
<td>0.51 (0.01)</td>
</tr>
<tr>
<td>Jaw osteonecrosis</td>
<td>18</td>
<td>9</td>
<td>— (0.08)</td>
</tr>
<tr>
<td>Grade 2-4 creatinine increase</td>
<td>11</td>
<td>5</td>
<td>— (0.46)</td>
</tr>
</tbody>
</table>
BUT A RECENT REVIEW ( JOP 2018 )

Use of Bone-Modifying Agents in Myeloma and Bone Metastases: How Recent Dosing Interval Studies Have Affected Our Practice

Erica Campagnaro, Melissa A. Reimers, Angel Qin, Ajjai S. Alva, Bryan J. Schneider, and Catherine H. Van Poznak
De-Escalation of Bone-Modifying Agents in Patients With Bone Metastases: The Best of Times and the Worst of Times?

Arif A. Awan, Alexander Paterson, and Mark Clemons
De-escalation of bone-modifying agents in patients with bone metastases from breast cancer: a systematic review and meta-analysis.

Awan AA¹, Hutton B², Hilton J¹, Mazzarello S³, Van Poznak C⁴, Vandermeer L³, Bota B³, Stober C³, Sienkiewicz M³, Fergusson D², Shorr R⁵, Clemons M⁶,7,8.
The menu

• Which guidelines, why?

• Messages from guidelines

• To conclude
Guidelines use can reduce health care costs

- Implementation of guidelines has resulted in observed improvements in care and absolute improvements in performance
- The reported degree of financial savings ranging from 6% to 57% (costs on drug, hospital, managing, etc.)
! Thank you!