Is hormone therapy really harmless in elderly people?

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IMO
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Dr Aapro is a consultant for Amgen, BMS, Celgene, GSK, Helsinn, JnJ Novartis, Merck, Merck Serono, Pfizer, Pierre Fabre, Roche, Sandoz, Teva, Vifor and has received honoraria for lectures at symposia of Amgen, Bayer Schering, Cephalon, GSK, Helsinn, Hospira, Ipsen, JnJ OrthoBiotech, Merck, Merck Serono, Novartis, Pfizer, Pierre Fabre, Roche, Sandoz, Sanofi, 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
Robert Coleman
Diana Crivellari
Arti Hurria
Juan Morote
Hans Wildiers

And many others
BREAKFAST MENU

• Why the elderly and why should hormonal therapy be harmless?

• About breast cancer

• About prostate cancer

• A common topic: bone health

• To conclude
Median age of global population is increasing...

Figure taken from: United Nations World Population Prospects at http://esa.un.org/unpp/index.asp?panel=2
...with increased age cancer incidence also increases

- A peak occurrence rate can be identified in high age groups
- Therefore cancer is a disease that affects a lot of elderly patients
- Evidence suggests that these patients often do not receive standard treatment

N Hebert-Croteau et al. Cancer 1999;85:1104-1113
CA Townsley et al. J Clin Oncol 2005;23:3112-3124
Image adapted from: CancerResearchUK.org accessed August 2010
We cannot “simply” apply principles of clinical studies validated in younger patients

EORTC workshop on clinical trial methodology in older individuals with a diagnosis of solid tumors

On behalf of the EORTC Elderly Task Force
Life expectancy in senior adults: a large variability reflecting health status variability

Life expectancy for elderly women based on health status

- Top 25th percentile (FIT seniors)
- 50th percentile (MEDIAN life expectancy)
- Lowest 25th percentile (FRAIL seniors)

Walters et al. JAMA 2001
Geriatric assessment

• General health and functional status for older individuals may be captured by collaborative geriatric and oncology management

• Active intervention for CGA-identified reversible deficits in geriatric domains may reduce morbidity and mortality, and improve quality of life

• Serial geriatric assessment may identify incident deterioration, for which intervention may improve outcomes
Comprehensive Geriatric Assessment (CGA)

- A well-established tool to assess the elderly patient for health status and risk of morbidity, mortality and toxicity\(^1\)

- Data suggest that CGA can improve patient treatment and outcome\(^2\)

- Breast cancer adj. chemotherapy can reduce relative death risk by 14–27%\(^3\)
  - If CGA suggests patients should receive beta blockers, it is possible that survival data will be affected
  - Beta blockers have reduced myocardial infarction relative mortality by 23%\(^4\)
  - Care is needed in balancing CGA assessments equally in arms of clinical studies

- Has limitations and is not always suitable for everyday use

---

Results (4)

**G8**
(Soubeyran et al. 2008)

- Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?
- Weight loss during the last 3 months
- Mobility
- Neuropsychological problems
- Body Mass Index (weight in kg/height in m²)
- Takes more than 3 medications per day
- In comparison with other people of the same age, how does the patient consider his/her health status?
- Age

**OS**

*Product-Limit Survival Estimates*
With Number of Subjects at Risk and 95% Hall-Wellner Bands

Kenis, …, Wildiers, J Clin Oncol, 2013
BREAKFAST MENU

• Why the elderly and why should hormonal therapy be harmless?

• About breast cancer

• About prostate cancer

• A common topic: bone health

• To conclude
The benefit of adjuvant tamoxifen is independent from patient’s age.

Breast cancer mortality/women

<table>
<thead>
<tr>
<th>Category</th>
<th>Deaths/women</th>
<th>Tamoxifen deaths</th>
<th>Ratio of annual death rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allocated tamoxifen:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adjusted control:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Logrank</td>
<td>Variance of O-E</td>
</tr>
<tr>
<td></td>
<td></td>
<td>O-E</td>
<td></td>
</tr>
<tr>
<td>(c) Entry age (trend $\chi^2_1 = 0.4; 2p &gt; 0.1; NS$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 40</td>
<td>74/417</td>
<td>-21.9</td>
<td>44.0</td>
</tr>
<tr>
<td></td>
<td>(17.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>119/398</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>173/1119</td>
<td>-24.8</td>
<td>90.3</td>
</tr>
<tr>
<td></td>
<td>(15.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>219/1139</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>330/1591</td>
<td>-45.2</td>
<td>161.7</td>
</tr>
<tr>
<td></td>
<td>(20.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>394/1535</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>379/1822</td>
<td>-87.3</td>
<td>200.4</td>
</tr>
<tr>
<td></td>
<td>(20.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>527/1789</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 70</td>
<td>62/266</td>
<td>-13.6</td>
<td>29.9</td>
</tr>
<tr>
<td></td>
<td>(23.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>89/286</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age unknown</td>
<td>0/10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0/14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EBCTCG. Lancet 2005
<table>
<thead>
<tr>
<th>Strategy</th>
<th>No.</th>
<th>Mean follow-up</th>
<th>Absolute decrease in recurrence</th>
<th>Absolute decrease in BC mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upfront</strong></td>
<td>9.856</td>
<td>5.8 yrs</td>
<td>At 5 yrs</td>
<td></td>
</tr>
<tr>
<td>ATAC</td>
<td>9.856</td>
<td>5.8 yrs</td>
<td>2.9% (SE=0.7%) 2P&lt;.00001</td>
<td>1.1% (SE=0.5%) 2P=.1</td>
</tr>
<tr>
<td>BIG 1-98</td>
<td>9.856</td>
<td>5.8 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sequential</strong></td>
<td>9.015</td>
<td>3.9 yrs</td>
<td>At 3 yrs from treatment divergence</td>
<td></td>
</tr>
<tr>
<td>ARNO</td>
<td>9.015</td>
<td>3.9 yrs</td>
<td>3.1% (SE=0.6%) 2P&lt;.00001</td>
<td>0.7% (SE=0.3%) 2P=.02</td>
</tr>
<tr>
<td>ABCSG-8</td>
<td>9.015</td>
<td>3.9 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IES</td>
<td>9.015</td>
<td>3.9 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITA</td>
<td>9.015</td>
<td>3.9 yrs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Which one to use?
(data not selected for the elderly)

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favor of AIs</th>
<th>In favor of tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flashes</td>
<td>(-5.3%)</td>
<td>(6.6%)</td>
</tr>
<tr>
<td>Weight gain*</td>
<td>(-1.8%)</td>
<td>(2.7%)</td>
</tr>
<tr>
<td>Vag. bleeding</td>
<td>(-3.9%)</td>
<td>(0.8%)</td>
</tr>
<tr>
<td>Vag. discharge</td>
<td>(-9.2%)</td>
<td></td>
</tr>
<tr>
<td>Endo Ca</td>
<td>(-0.4%)</td>
<td></td>
</tr>
<tr>
<td>Ischemic cerebrovascular acc.</td>
<td>(-1.1%)</td>
<td></td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>(-1.4%)</td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>(-0.7%)</td>
<td></td>
</tr>
</tbody>
</table>

Difference between AI and tamoxifen AEs, %

Musculoskeletal disorders
Fractures
Fractures of hip, spine, wrist

*Proportion with ≥10% gain in body weight from baseline to year 2.

# Safety profile

<table>
<thead>
<tr>
<th>Tamoxifen</th>
<th>Aromatase inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial cancer</td>
<td>Musculoskeletal events</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>Decreased bone mineral densitometry and bone fractures</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular events</td>
</tr>
</tbody>
</table>

**Comorbidities**

- Thromboembolism?
- Osteoporosis?
- Ischemic heart disease?
- Arthralgia?
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
Cardiovascular Considerations in Elderly Patients

- Cardiovascular associated co-morbidities are common
- Tamoxifen is known to have a favorable effect on cholesterol but is associated with an increase in thromboembolic events
- Thromboembolic events are not associated with AI treatment
  - Most trials have not linked hypercholesterolemia with the use of AIs and a sub-study of the TEAM trial actually reported a decrease in cholesterol levels associated with exemestane treatment

Longer duration of AI use is associated with statistically significant increase in the odds of developing cardiovascular disease compared with TAM alone or shorter duration of AI use (OR 1.26; 95% CI 1.10-1.43, P<.001)

4.2% of patients in the AI group and 3.4% of patients in the TAM group suffered a cardiovascular event (difference in absolute risk=0.8%)
Specific subpopulations might be at higher risk

- ATAC: in women with preexisting heart disease (7.5% of the total trial population) the incidence of cardiovascular events was 17% with anastrozole and 10% with tamoxifen ¹

- MA.17: In multivariable analyses, a treatment interaction was found with cardiovascular disease and a detrimental effect was observed with letrozole administration (\( P < .001 \)) among patients who had cardiovascular disease at baseline ²

Tamoxifen vs aromatase inhibitors in elderly patients: safety

- Comorbidities present in older women might increase the risk of some AI’s related side-effects
- Tamoxifen’s side effects are correlated with age:
  - There is little uterine cancer risk or excess risk of fatal pulmonary embolus from administration of tamoxifen before age 45 years or at ages 45–54 years¹
  - By contrast, for older women with an intact uterus the excess risk of death from endometrial cancer or pulmonary embolus could well be about 1%²

Aromatase Inhibitors and Tamoxifen: Potential Risks and Benefits

- Contralateral BC
- Osteoporosis risk
- Myalgia
- Hyperlipidemia
- Neurocognition
- Sexual function
- Cardiovascular disease

Tamoxifen:
- Hot flashes
- Thromboembolism
- Endometrial cancer
- Genitourinary adverse effects

Aromatase Inhibitor:
- Arthralgia/myalgia
- Osteoporosis risk
- Deep vein thrombosis
- Endometrial cancer
- Hot flashes
Cognitive functioning and HT

- Older age is often associated with cognitive decline and endocrine therapy may adversely affect cognitive functioning
- Tamoxifen has been shown to negatively impact cognitive functioning
- A sub-study of the TEAM trial and another of the BIG 1-98 trial show that letrozole or exemestane do not significantly impact cognitive functioning when compared to Tamoxifen or healthy control subjects
  - Tamoxifen users, on the other hand, performed significantly worse on verbal memory and executive functioning when compared to healthy controls.

Tolerability profile of HT

- **Tamoxifen has a well defined adverse event profile**
  - Treatment is associated with increased gynecological events such as endometrial carcinoma and vaginal bleeding, thromboembolic events are also frequently reported
  - Tamoxifen has been shown to have a positive effect on bone and lipid profile

- **AIs have a different AE profile when compared to tamoxifen**
  - AI treatment is not associated with endometrial carcinoma or thromboembolic events
  - However, AIs are reported to cause more musculoskeletal AEs and are reported to cause more osteoporosis and a higher risk of fractures.

BREAKFAST MENU

• Why the elderly and why should hormonal therapy be harmless?

• About breast cancer

• About prostate cancer

• A common topic: bone health

• To conclude
Management of advanced prostate cancer: Specific considerations for senior adults

• **First-line ADT monotherapy** is the standard of care

![Graph showing survival rates](image)

8000 prostate cancer patients in 27 trials of antiandrogen (nilutamide, flutamide, or cyproterone acetate)

- Androgen suppression only
- Androgen suppression + antiandrogen

**Proportion alive (%)**

- 80: 25.4%
- 60: 23.6%
- 40: Absolute difference 1.8% (SE 1.3)
- 20: Treatment better by 0.7% (SE 1.1) Logrank 2p>0.1
- 10: 6.2%

**Time since randomisation (years)**

- 0
- 5
- 10

**OS:** Overall survival

**QoL:** Quality of life


Maximum androgen blockade results in a small advantage in OS, which is not clinically relevant

Maximum androgen blockade has significant effects on QoL

OS: Overall survival QoL: Quality of life.
Androgen deprivation therapy: Side effects

- Bone loss with increased risk of fracture\(^1,2\)
- Baseline bone density
- Prevent risk of osteoporosis

- Increased risk of diabetes\(^3\)
- Increased risk of fatal cardiac events\(^4–6\)

Caution in patients with:
- History of stroke
- Chronic heart failure
- Myocardial infarction

LESS is BETTER ...

## Side effects of ADT

<table>
<thead>
<tr>
<th>Visible</th>
<th>Non-visible</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most common</strong></td>
<td><strong>What you see</strong></td>
</tr>
<tr>
<td>• Loss of libido</td>
<td>• Weight gain</td>
</tr>
<tr>
<td>• Erectile dysfunction</td>
<td>• Gynaecomastia</td>
</tr>
<tr>
<td>• Hot flushes</td>
<td>• Loss of muscle mass, strength</td>
</tr>
<tr>
<td></td>
<td>• Decreased size – penis and testes</td>
</tr>
<tr>
<td></td>
<td>• Hair changes</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>


BREAKFAST MENU

• Why the elderly and why should hormonal therapy be harmless?

• About breast cancer

• About prostate cancer

• A common topic: bone health

• To conclude
Osteoporosis in Elderly Patients

- Bone density decreases with age
- AI treatment and ADT are associated with an increased risk of osteoporosis. Tamoxifen is somewhat “protective”
- Treatment induced bone loss can be managed with additional medication such as vitamin D and calcium supplements and bisphosphonates/denosumab
- AI induced decrease in bone density reverses after treatment termination

RE Coleman et al. Breast Cancer Res Treat. 2010
AI therapy is associated with rapid bone loss

Data from a substudy of ATAC (similar data with all AIs)

Iatrogenic effects of androgen deprivation on the skeleton in prostate cancer patients

Approximately 2000 osteoporosis-induced fractures in the US every year

GnRH agonists and time to first fracture

![Graph showing the proportion without fracture over time for different groups of patients treated with GnRH agonists.](https://example.com/graph.png)

- No GnRH agonist (n = 7774)
- GnRH agonist < 1 yr (n = 1368)
- GnRH agonist ≥ 1 yr (n = 2519)

CTIBL is more rapid than naturally occurring bone loss

Bone loss induced by ADT for prostate cancer is rapid and clinically significant

- Naturally occurring bone loss
- CTIBL

<table>
<thead>
<tr>
<th>Condition</th>
<th>Bone Loss at 1 Year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal men</td>
<td>0.5</td>
</tr>
<tr>
<td>Postmenopausal women &gt; 55 yrs</td>
<td>1.0</td>
</tr>
<tr>
<td>Menopausal women &lt; 55 yrs</td>
<td>2.0</td>
</tr>
<tr>
<td>AI Therapy in postmenopausal women</td>
<td>2.6</td>
</tr>
<tr>
<td>ADT</td>
<td>4.6</td>
</tr>
<tr>
<td>AI Therapy + GnRH agonist in premenopausal women</td>
<td>7.4</td>
</tr>
<tr>
<td>Premature menopause secondary to chemotherapy</td>
<td>7.7</td>
</tr>
</tbody>
</table>

Prevalence of Osteoporosis During Long-Term Androgen Deprivation Therapy in Patients with Prostate Cancer

Juan Morote, Jacques Planas Morin, Anna Orsola, Jose M. Abascal, Carles Salvador, Enrique Trilla, Carles X. Raventos, Lluís Cecchini, Gloria Encabo, and Jaume Reventos

Characteristics of bone mass loss in prostate cancer patients on ADT

- Intense during the first year
- Slows after the second year
- Continuous over 10 years
SKELETAL FRACTURES NEGATIVELY CORRELATE WITH OVERALL SURVIVAL IN MEN WITH PROSTATE CANCER.

MICHAEL G. OEFELEin, VINCENT RICCHIUTI, WILLIAM CONRAD AND MARTIN I. RESNICK

From the Department of Urology, University Hospitals of Cleveland, Case Western Reserve School of Medicine, Cleveland, Ohio

- 24/195 (12.3%)
- 5/24 (20.8%) pathologic
- 10/24 (41.7%) osteoporotic
- 9/24 (37.5%) before ADT ??

Fractures and post-fracture mortality in prostate cancer patients receiving ADT

- Analysis from SEER database, N = 72,400 pts with PCa diagnosed 1996–2003

<table>
<thead>
<tr>
<th></th>
<th>Orchidectomy</th>
<th>LHRH-agonist during first 6 mo after diagnosis</th>
<th>No ADT during FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>2.2%</td>
<td>47.2%</td>
<td>50.6%</td>
</tr>
<tr>
<td>Fracture risk (HR, 95% CI)</td>
<td>1.7 (1.5–1.9)</td>
<td>1.3 (1.3–1.4)</td>
<td>1</td>
</tr>
<tr>
<td>Fractures resulting in hospitalisation (HR, 95% CI)</td>
<td>1.9 (1.6–2.3)</td>
<td>1.4 (1.3–1.5)</td>
<td>1</td>
</tr>
</tbody>
</table>

- Fractures resulting in hospitalisation were associated with increased mortality (HR: 1.2, 95% CI: 1.2–1.3)

PCa pts receiving ADT are at increased risk of fractures; fractures resulting in hospitalisation are associated with a 20% increase in risk of mortality

Cetin K. J Clin Oncol 2010:28(15S):356s(abs.4559)
Consequences of CTIBL

- Reduced overall strength of the bone and loss of BMD leads to bone fragility and increased susceptibility to fractures

- Common sites
  - Femoral neck
  - Radius
  - Vertebral spine
  - Lumbar spine

- Fractures are associated with increased mortality

- Because natural restoration of bone is limited, prevention, early diagnosis and treatment of CTIBL are essential to improve patient outcome and quality of life

Pharmacological prevention of bone mass loss during ADT

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Duration</th>
<th>No pts</th>
<th>Endpoints</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith, et al J Urol 2003</td>
<td>Zoledronate (IV 4 mg Q3M) vs placebo</td>
<td>One year</td>
<td>106</td>
<td>% change BMD lumbar spine</td>
<td>+5.6 zoledronate vs -2.2 placebo</td>
</tr>
<tr>
<td>Michelson, et al J Clin Oncol 2007</td>
<td>Zolodronate (IV 4 mg on day one) vs placebo</td>
<td>One year</td>
<td>40</td>
<td>% change BMD lumbar spine</td>
<td>+4.0% zoledronate vs -3.1 placebo</td>
</tr>
<tr>
<td>Greenspan, et al Ann Int Med 2007</td>
<td>Alendronate oral (70 mg Q1W) vs placebo</td>
<td>One year</td>
<td>112</td>
<td>% change BMD lumbar spine</td>
<td>+3.7 alendronate vs -1.4 placebo</td>
</tr>
<tr>
<td>Smith, et al N Eng J Med 2009</td>
<td>Denosumab (SC 60 mg Q6M) vs placebo</td>
<td>Three years</td>
<td>1468</td>
<td>% change BMD lumbar spine and vertebral fractures*</td>
<td>+5.5 denosumab vs -1 placebo (24m) 1.5% denosumab vs 3.9% denosumab (36m)</td>
</tr>
</tbody>
</table>

*FDA Good Guidance Practice guidelines for preclinical and clinical evaluation of agents used in the prevention or treatment of postmenopausal osteoporosis 1997

*EMEA guideline on the evaluation of new medicinal products in the treatment of primary osteoporosis 2005.

Denosumab is the only agent licensed for this indication.
Denosumab in men receiving ADT for prostate cancer

Mean percent changes in BMD from baseline

**Lumbar Spine**

Placebo (n = 734) vs Denosumab (n = 734)

- **Study Month**: 0 1 3 6 12 24 36
- **Placebo (n = 734)**
- **Denosumab (n = 734)**

6.7% difference at 24 mo\(^a\)

*P ≤ .001 at all measured sites

\(^a\)Primary end point

**Total Hip**

Placebo (n = 734) vs Denosumab (n = 734)

- **Study Month**: 0 1 3 6 12 24 36
- **Placebo (n = 734)**
- **Denosumab (n = 734)**

4.8% difference at 24 mo

Denosumab in men receiving ADT for prostate cancer

Cumulative incidence of new vertebral fracture

Placebo (n = 673)  SC Denosumab (n = 679)

<table>
<thead>
<tr>
<th>Month</th>
<th>Placebo</th>
<th>SC Denosumab</th>
<th>RR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>1.9%</td>
<td>0.3%</td>
<td>0.15</td>
<td>.004</td>
</tr>
<tr>
<td>24</td>
<td>3.3%</td>
<td>1.0%</td>
<td>0.31</td>
<td>.004</td>
</tr>
<tr>
<td>36</td>
<td>3.9%</td>
<td>1.5%</td>
<td>0.38</td>
<td>.006</td>
</tr>
</tbody>
</table>

RR = relative risk.

Post-hoc analysis: Higher death rate in patients with vertebral fracture

Adapted from Smith MR, et al. ECCO-ESMO 2009; Abstract 7005
Specific considerations for senior adults

Abiraterone

- Hypokalaemia, hypertension & fluid retention due to mineralocorticoid excess
  Use with caution in patients with cardiovascular diseases

- Adrenocortical insufficiency
  Caution after interruption of daily steroids and/or concurrent infection or stress

- Hepatotoxicity
  Monitor liver function
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.
BPs Decrease Mortality In Post-menopausal Women

**Breast cancer mortality**

- 11036 women
- 1146 events

10–y gain 3.1% (SE 1.3)
Logrank 2p = 0.004

**All cause mortality**

- 11036 women
- 1524 events

10–y gain 2.3% (SE 1.5)
Logrank 2p = 0.007

Death rates (% / year) and logrank analyses

**Breast cancer mortality**

<table>
<thead>
<tr>
<th>Allocation</th>
<th>Years 0 – 4</th>
<th>Years 5 – 9</th>
<th>Year 10+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisph</td>
<td>1.64 ± 0.08</td>
<td>1.60 ± 0.14</td>
<td>1.30 ± 0.49</td>
</tr>
<tr>
<td>Not</td>
<td>1.83 ± 0.09</td>
<td>2.04 ± 0.16</td>
<td>2.73 ± 0.73</td>
</tr>
<tr>
<td>Rate ratio, from (O–E) / V</td>
<td>0.66 ± 0.07</td>
<td>0.78 ± 0.11</td>
<td>0.52 ± 0.38</td>
</tr>
</tbody>
</table>

**All cause mortality**

<table>
<thead>
<tr>
<th>Allocation</th>
<th>Years 0 – 4</th>
<th>Years 5 – 9</th>
<th>Year 10+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisph</td>
<td>2.07 (510 / 24627)</td>
<td>2.40 (201 / 8380)</td>
<td>2.88 (236 / 8189)</td>
</tr>
<tr>
<td>Not</td>
<td>2.32 (534 / 23006)</td>
<td>2.88 (236 / 8189)</td>
<td>4.48 (23 / 513)</td>
</tr>
<tr>
<td>Rate ratio, from (O–E) / V</td>
<td>0.87 ± 0.06</td>
<td>0.84 ± 0.09</td>
<td>0.94 ± 0.34</td>
</tr>
</tbody>
</table>

Death rates (% / year) total rate = rate in women without recurrence & logrank analyses

<table>
<thead>
<tr>
<th>Allocation</th>
<th>Years 0 – 4</th>
<th>Years 5 – 9</th>
<th>Year 10+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisph</td>
<td>2.71 (20) / 539</td>
<td>3.12 (20) / 539</td>
<td>4.48 (23) / 513</td>
</tr>
<tr>
<td>Not</td>
<td>3.12 (20) / 539</td>
<td>3.09 (20) / 539</td>
<td>4.48 (23) / 513</td>
</tr>
<tr>
<td>Rate ratio, from (O–E) / V</td>
<td>0.84 ± 0.09</td>
<td>0.84 ± 0.09</td>
<td>0.94 ± 0.34</td>
</tr>
</tbody>
</table>

Not 23.8%
21.5% Bisph
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”
Prevention of bone loss in patients with treatments known to increase the risk of fractures

- Baseline fracture risk factor assessment
  - e.g. age >65 years, smoking, oral corticosteroid use >6 months, low BMI (<20), family history of hip-fracture, personal history of fragility fracture after age 50

- Bone mineral density (BMD) measurement

- Lifestyle changes
  - Take more weight-bearing exercise
  - Stop smoking
  - Reduce alcohol consumption

- Dietary measures and supplements
  - Adequate calcium (1000 mg/day) intake
  - Supplementary vitamin D (to total intake of 1000–2000 units/day)

- In selected cases – bone directed anti-resorptive therapy to manage low BMD or rapid bone loss

# Diagnosis: Recommended techniques

<table>
<thead>
<tr>
<th><strong>Isotope bone scan</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sensitive test used to detect presence of skeletal pathology</td>
<td></td>
</tr>
<tr>
<td>• Gives little information about nature of damage/metastatic disease</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>CT and MRI</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Recommended for obtaining structural information on skeletal damage from metastatic bone disease</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>PET</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Provides functional information that may aid in diagnosis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>DXA scan</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Recommended for patients at risk of fracture or cancer treatment-induced bone loss</td>
<td></td>
</tr>
</tbody>
</table>

**Plain radiographs**

• *An insensitive test for metastasis – lesions need to be >1cm with bone mineral loss of ~50% to be recognized*
Patient evaluation

**Patient examination**
- Assessment of symptoms and activity status is essential

**Skeletal radiography**
- Used to assess response to treatment, and fractures
- But structural changes are slow to evolve and the method is insensitive

**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

Regulatory approval for anti-resorptive agents in cancer patients

<table>
<thead>
<tr>
<th>Indication</th>
<th>Regulatory approval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevention of skeletal-related events</strong></td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid 4 mg i.v. every 3–4 weeks</td>
<td>All solid tumours and multiple myeloma</td>
</tr>
<tr>
<td>Denosumab 120 mg s.c. every 4 weeks</td>
<td>All solid tumours</td>
</tr>
<tr>
<td>Pamidronate 90 mg i.v. every 3–4 weeks</td>
<td>Breast cancer and multiple myeloma</td>
</tr>
<tr>
<td>Clodronate 1600 mg p.o. daily</td>
<td>Osteolytic lesions*</td>
</tr>
<tr>
<td>Ibandronate 50 mg p.o. daily</td>
<td>Breast cancer*</td>
</tr>
<tr>
<td>Ibandronate 6 mg i.v. monthly</td>
<td>Breast cancer*</td>
</tr>
<tr>
<td><strong>Prevention of breast cancer metastases</strong></td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid 4 mg i.v. 6 monthly</td>
<td>None</td>
</tr>
<tr>
<td>Zoledronic acid 4 mg i.v. monthly x 6, then 3–6 monthly</td>
<td>None</td>
</tr>
<tr>
<td>Clodronate 1600 mg daily</td>
<td>None</td>
</tr>
<tr>
<td><strong>Prevention of prostate cancer metastases</strong></td>
<td></td>
</tr>
<tr>
<td>Denosumab 120 mg s.c. monthly</td>
<td>None</td>
</tr>
<tr>
<td><strong>Prevention of treatment-induced bone loss</strong></td>
<td></td>
</tr>
<tr>
<td>Denosumab 60 mg s.c. 6 monthly</td>
<td>Prostate and breast cancer</td>
</tr>
<tr>
<td>Zoledronic acid 4 mg i.v. 6 monthly</td>
<td>None</td>
</tr>
<tr>
<td>Alendronate 70 mg p.o. weekly</td>
<td>None</td>
</tr>
<tr>
<td>Risedronate 35 mg p.o. weekly</td>
<td>None</td>
</tr>
<tr>
<td>Ibandronate 150 mg p.o. monthly</td>
<td>None</td>
</tr>
<tr>
<td>Pamidronate 90 mg i.v. every 3 months</td>
<td>None</td>
</tr>
</tbody>
</table>

*European approval only (not US)
i.v. – intravenous; s.c. subcutaneous; p.o. per oral
Treatment recommendations

Prevention of treatment-induced bone loss

- Bisphosphonates and denosumab prevent bone loss associated with ovarian suppression/aromatase inhibitors in early breast cancer and androgen deprivation therapy in prostate cancer

ESMO recommended algorithm for managing bone health during 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 risk factors:
- 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; denosumab may be a potential treatment option in some patients)
- Monitor BMD every 2 years
- Check compliance with oral therapy
BREAKFAST MENU

• Why the elderly and why should hormonal therapy be harmless?

• About breast cancer

• About prostate cancer

• A common topic: bone health

• To conclude
Hormone therapy is not harmless but one can decrease its toxicity.
THANK YOU to all the patients and their physicians, nurses and carers