Anthracyclines in the elderly breast cancer patients

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Facts about anthracyclines

• Cornerstone for treatment of MBC and EBC

<table>
<thead>
<tr>
<th></th>
<th>Relapse</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Relative</td>
</tr>
<tr>
<td>Anthracyclines &gt; CMF</td>
<td>6950</td>
<td>12 ± 4</td>
</tr>
</tbody>
</table>

However, mainly < 60 years since very few data beyond

- Chemotherapy  < 5%  1224/28764
- Anthracyclines < 2%  213/14971

EBCTCG. Lancet 1998 & 2005
Anthracyclines cardiotoxicity

- Oxydative stress: multiple irreversible & cumulative damage to myocytes
- Rare acute toxicity
- Dilated cardiomyopathy
  - Insidious subclinical
  - Systolic dysfunction
  - Left sided CHF
  - Occurrence @ 2-5 years > treatment
  - Median survival ~ 1 year
- Early signs
  - Impaired diastolic function
  - Biomarkers (CK-MB, NT-proBNP)

CHF induced by anthracyclines

<table>
<thead>
<tr>
<th>Cause</th>
<th>HR</th>
<th>(95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>1.00</td>
<td>(0.99-1.01)</td>
<td>0.27</td>
</tr>
<tr>
<td>Peripartum</td>
<td>0.31</td>
<td>(0.27-0.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.74</td>
<td>(0.66-0.83)</td>
<td>0.001</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>1.05</td>
<td>(0.67-1.61)</td>
<td>0.82</td>
</tr>
<tr>
<td>Connective disease</td>
<td>1.75</td>
<td>(1.02-3.01)</td>
<td>0.04</td>
</tr>
<tr>
<td>Ischemic heart</td>
<td>1.52</td>
<td>(1.07-2.17)</td>
<td>0.02</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>3.46</td>
<td>(1.67-7.18)</td>
<td>0.001</td>
</tr>
<tr>
<td>HIV</td>
<td>5.86</td>
<td>(3.92-8.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infiltrative myocardial disease</td>
<td>4.40</td>
<td>(3.04-6.39)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Co-morbidity across age

Co-morbidity @ AgeingStats.Gov

Percentage of people age 65 and over who reported having selected chronic conditions, by sex, 2005–2006

- Heart disease
  - Men: 37
  - Women: 26
- Hypertension
  - Men: 52
  - Women: 54
- Stroke
  - Men: 10
  - Women: 8
- Asthma
  - Men: 10
  - Women: 12
- Chronic bronchitis or Emphysema
  - Men: 11
  - Women: 10
- Any cancer
  - Men: 24
  - Women: 19
- Diabetes
  - Men: 19
  - Women: 17
- Arthritis
  - Men: 43
  - Women: 54

Note: Data are based on a 2-year average from 2005–2006.
Reference population: These data refer to the civilian noninstitutionalized population.
Source: Centers for Disease Control and Prevention, National Center for Health Statistics, National Health Interview Survey.

http://www.agingstats.gov/Agingstatsdotnet/Main_Site/Data/2008_Documents/Health_Status.aspx
Competing causes of mortality

Deaths attributed to the primary cancer (solid dots) and those attributed to comorbidity (open circles)

Kendal. Cancer 2008
DXR, CHF and age

- 630 patients (3 phase III) with 32 CHF
  - 26% >550 mg/m²
  - >50%: reduction of LVEF <30% w/CT
- HR\textsubscript{age} 2.25 (1.04–4.86) vs 3.28 (1.4–7.65) if >400 mg/m²

Swain. Cancer 2003
Doxorubicin, CHF and age

  - stage I to III BC, chemotherapy vs no
  - AC: younger, fewer comorbidities, advanced ($p=0.001$)
  - $\text{CHF}_{10\text{ years}}$ (%)

<table>
<thead>
<tr>
<th></th>
<th>AC</th>
<th>Other chemo</th>
<th>No chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>4,712</td>
<td>3,921</td>
<td>34,705</td>
</tr>
<tr>
<td>CHF (%)</td>
<td>38.4</td>
<td>32.5</td>
<td>29</td>
</tr>
</tbody>
</table>

- 66-70 years HR 1.26 (95% CI, 1.12-1.42) if AC
- 71-80 years no impact of CT type

Baseline | HR    | (95% CI) |
---------|-------|----------|
Age (decade) | 1.79  | (1.66-1.93) |
Black | 1.40  | (1.30-1.50) |
Trastuzumab | 1.46  | (1.21-1.77) |
Hypertension | 1.45  | (1.39-1.52) |
Diabetes | 1.74  | (1.66-1.83) |
Coronary | 1.58  | (1.39-1.79) |
Left XRT | 1.04  | (0.98-1.11) |

Trastuzumab cardiotoxicity

Table 5. Summary of cardiac toxicity in randomized trials with adjuvant trastuzumab in early breast cancer patients

<table>
<thead>
<tr>
<th></th>
<th>NSABP B31 [113]</th>
<th>N9831 [114]</th>
<th>HERA [112]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AC→T</td>
<td>AC→TH</td>
<td>AC→T</td>
</tr>
<tr>
<td>CHF NYHA class 3–4</td>
<td>3</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Cumulative incidence at 3 years</td>
<td>0.6%</td>
<td>4%</td>
<td>NA</td>
</tr>
<tr>
<td>Cardiac deaths</td>
<td>1</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: AC, doxorubicin and cyclophosphamide; CHF NYHA class 3–4, congestive heart failure New York Heart Association class 3–4; H, trastuzumab; HERA, HERceptin® Adjuvant; NSABP, National Surgical Adjuvant Breast and Bowel Project; NA, not available; Obs, observation arm; T, paclitaxel; TH, paclitaxel and trastuzumab.

HERA

- LVEF decrease 3% vs 0.5%
- CHF 2.1% vs 0.2%

Influence (NSABP B31)

- Age (2% <50 years vs 5.4% >60 years)
- LVEF >4 AC (12% if LVEF <55%)
- Concomitant > sequential
- Inhibition of a HER2-mediated cardioprotective mechanism?

Colozza. Oncologist 2006; Geyer. ASCO 2006; Smith. ASCO 2006
DXR, PK and age

- 37 patients w/DXR
- 110 patients w/DXR
- CL 63.6+/−22.7 L/h
- No Δ according to age

Early clearance 1. h⁻¹, m⁻²

Age (years)

p<0.0005

DXR, tolerance and age

MDA 1974–1988
- 390 patients >50 years EBC
- DXR 40 mg/m²
  - 325 patients 50–64 years
    - FU 185 months (29–272+)
  - 65 patients >65 years
    - FU 169 months (128–240+)

No difference according to age
- PS, HR, pT, pN, surgery, relapse, DFS, OS
- Nadirs neutrophils + platelets at C_{1,3,6}
- Cumul of haematological toxicity
- Doses really administered?

MDA 1973–1984
- 1011 MBC
- DXR 50 mg/m²

Difference according to age
- RR, fever (12% vs 17%)

No difference according to age
- OS, TTP, DI
- Nadirs neutrophils and platelets, FN (16%), toxic deaths/infection (3.2%)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>50–64 years</th>
<th>&gt;65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>767</td>
<td>244</td>
</tr>
<tr>
<td>% median dose administered</td>
<td>91.5</td>
<td>80</td>
</tr>
<tr>
<td>&gt;85% dose received (%)</td>
<td>52</td>
<td>46</td>
</tr>
</tbody>
</table>

Decrease risk of CHF

- Infusion (≥6 hr vs shorter)
  - HR 0.27 (95% CI 0.09-0.81)

Decrease risk of CHF

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  - HR 0.27 (95% CI 0.09-0.81)
- Analogs (epirubicin)
  - HR 0.36 (95% CI 0.12-1.11)
  - Efficacy dose/dose?

Adjuvant chemotherapy

- 338 patients >65 years (3.1991–4.2001)
- TAM$_{30\,\text{mg}}$ 3 yrs vs TAM$_{30\,\text{mg}}$ 3 yrs + E$_{30\,\text{mg}}$ J1J8J15 q4w x 6 Cy

**Disease-free survival (prob)**

- TAM: 69.3% (tamoxifen [TAM])
- EPI-TAM: 72.6% (epirubicin plus TAM [EPI-TAM]); $p=0.14$ (univariate) and $p=0.006$ (multivariate)

**Overall survival (prob)**

- TAM: 75.8% (tamoxifen [TAM])
- EPI-TAM: 75.4% (epirubicin plus TAM [EPI-TAM]); $p=0.81$

Fargeot. J Clin Oncol 2004
Decrease risk of CHF

- Infusion (≥6 hr vs shorter)
  - HR 0.27 (95% CI 0.09-0.81)
- Analogs (epirubicin)
  - HR 0.36 (95% CI 0.12-1.11)
  - Efficacy dose/dose?
- Liposomal formulations
  - HR 0.20 (95% CI 0.05-0.75)
  - HR 0.38 (95% CI 0.24-0.59)
    - subclinical

Non pegylated liposomal DXR

• Reduces cardiotoxicity

<table>
<thead>
<tr>
<th></th>
<th>AC</th>
<th>MC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiotoxicity (%)</td>
<td>24</td>
<td>6</td>
<td>.0002</td>
</tr>
<tr>
<td>Median cumulative DXR dose (mg/m²)</td>
<td>480</td>
<td>2,220</td>
<td>.0001</td>
</tr>
<tr>
<td>Median TTP (mth)</td>
<td>5.5</td>
<td>5.1</td>
<td>NS</td>
</tr>
<tr>
<td>Median TTF (mth)</td>
<td>4.4</td>
<td>4.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

• Maintenance of anti-tumour effect

• Privileged position given the combination w/other targeted cardiotoxic agents (HER2+)

Decrease risk of CHF

- Infusion (≥6 hr vs shorter)
  - HR 0.27 (95% CI 0.09-0.81)
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  - HR 0.20 (95% CI 0.05-0.75)
  - HR 0.38 (95% CI 0.24-0.59) subclinical
- Iron chelating agent dexrazoxane
  - HR 0.29 (95% CI 0.20-0.44)
- β- and ACE inhibitors

Decrease risk of CHF

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  - HR 0.27 (95% CI 0.09-0.81)
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  - HR 0.36 (95% CI 0.12-1.11)
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  - HR 0.38 (95% CI 0.24-0.59) subclinical
- Iron chelating agent dexrazoxane
  - HR 0.29 (95% CI 0.20-0.44)
- β- and ACE inhibitors
- Replace AC in adjuvant and metastatic settings

Fig 1. Disease-free survival (DFS) and overall survival (OS) (A) DFS by treatment; (B) DFS by treatment and age; (C) OS by treatment: 1 day; (D) OS by treatment and age

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>% by Age Group</th>
<th>&lt; 65</th>
<th>≥ 65</th>
<th>&lt; 65</th>
<th>≥ 65</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TC (n = 428)</td>
<td>AC (n = 428)</td>
<td>TC (n = 78)</td>
<td>AC (n = 82)</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>&lt; 1</td>
<td>1</td>
<td>&lt; 1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>60</td>
<td>54</td>
<td>52</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>&lt; 1</td>
<td>1</td>
<td>0</td>
<td>&lt; 1</td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4</td>
<td>2</td>
<td>8</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>1</td>
<td>&lt; 1</td>
<td>0</td>
<td>&lt; 1</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>4</td>
<td>3</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Infecion</td>
<td>7</td>
<td>10</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>&lt; 1</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1</td>
<td>1</td>
<td>&lt; 1</td>
<td>&lt; 1</td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>&lt; 1</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>7</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Phlebitis</td>
<td>&lt; 1</td>
<td>&lt; 1</td>
<td>&lt; 1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: TC, docetaxel/cyclophosphamide; AC, doxorubicin/cyclophosphamide.
CALGB / CTSU 49907

- 9/2001-12/2006
- 633 pts ≥ 65 yo
  - 65% 70+
  - 55% pT > 2 cm
  - 71% pN+
  - 68% ER+
- Non-inferiority trial
- Median follow up 2.4 years
- Capecitabine vs standard
  - RFS$_{3A}$ 68% vs 85%
  - OS$_{3A}$ 86% vs 91%
  - Toxicity 33% vs 64%
- Capecitabine
  - 76% compliance (> 80%)
- AC & CMF > capecitabine
  - Interaction +++ if ER-
  - $HR_{RFS}$ 4.39 (95% CI: 2.9-6.7)
  - $HR_{OS}$ 3.76 (95% CI: 2.23-6.34)

Muss NEJM 2009
Figure 1. Kaplan-Meier Estimates of Relapse-free and Overall Survival According to Treatment Group.

Relapse-free survival (Panel A) and overall survival (Panel B) for all patients are shown. Panel C shows relapse-free survival for patients with hormone-receptor–positive tumors, and Panel D shows relapse-free survival for patients with hormone-receptor–negative tumors. Panel E shows overall survival for patients with hormone-receptor–positive tumors, and Panel F shows overall survival for patients with hormone-receptor–negative tumors. AC denotes doxorubicin plus cyclophosphamide, and CMF: cyclophosphamide, methotrexate, and fluorouracil.
### Adjuvant chemotherapy and mortality

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. total</td>
<td>41,390</td>
<td>5,081</td>
</tr>
<tr>
<td></td>
<td>No. w/CT</td>
<td>4,500</td>
<td>1,711</td>
</tr>
<tr>
<td>pN0</td>
<td>∀</td>
<td>1.05 (0.85-1.31)</td>
<td>NA</td>
</tr>
<tr>
<td>pN+</td>
<td>+</td>
<td>1.05 (0.85-1.31)</td>
<td>NA</td>
</tr>
<tr>
<td>both</td>
<td>-</td>
<td>NA</td>
<td>0.85 (0.77-0.95)</td>
</tr>
<tr>
<td>pN+</td>
<td>-</td>
<td>0.72 (0.54-0.96)</td>
<td>0.76 (0.65-0.88)</td>
</tr>
<tr>
<td>pN+ &gt; 70 yo</td>
<td>-</td>
<td>0.74 (0.56-0.97)</td>
<td></td>
</tr>
</tbody>
</table>

*: BC specific mortality

**Adjuvant chemo is useful in ER-, pN0 or pN+, even > 70 yo**

Summary

- No good evidence base
  - Need for randomized trials specific to elderly
  - Analyses « post hoc » whenever possible

- Sufficient life expectancy
  - For benefit from a reduced rate of tumour recurrence
  - For long term toxicities to become apparent

- Over vs under treatment!

- Cardiotoxicity
  - Rigorous monitoring and early intervention
  - Risk factors
    - Hypertension, CHF, diabetes, coronary disease
    - Old age
    - AC (cumulative), trastuzumab

- Less cardiotoxic schedules
  - Long infusion but burden!!
  - Liposomal
  - Careful w/HER2
  - Different settings+++  
    - EBC: use maximal ressources for prevention
    - MBC: alternatives