BREAST CANCER AS A CHRONIC DISEASE
incidence, patient and treatment characteristics

Ana Cvetanovic
Clinic of Oncology
Clinical Centre of Nis, Serbia

UMOS, Hotel M, 16-17 May 2015, Belgrade
Mortality in Serbia (females) 2010

Vodeće lokalizacije u umiranju od malignih tumora kod žena, centralna Srbija, 2010. god.
The leading cancer sites, deaths, females in Central Serbia, 2010

- Mozak (C71) Brain 3.5%
- Leukemije (C91-C95) Leukaemias 2.9%
- Jetra (C22) Liver 2.8%
- Želudac (C16) Stomach 4.3%
- Ovarijum (C56) Ovary 4.6%
- Grlić materice (C53) Cervix uteri 5.7%
- Pankreas (C25) Pancreas 5.9%
- Kolon/rectum (C18-C20) Colon & rectum 11.0%
- Pluća/bronh (C34) Lung & bronchus 13.9%
- Materica, telo (C54) Corpus uteri 2.4%
- Druge lokalizacije Other sites 24.5%
- Dojka (C50) Breast 18.6%
British Columbia Population Based Data
Hazard Rate of Relapse According to Tumor Subtype and Year of Diagnosis

Survival of mBC

MDA experience 1974 - 2000

No. of drug available

Metastatic breast cancer

- The survival of pts with metastatic disease is improving with new therapeutic options
- MBC is still incurable, but highly treatable, chronic disease

The goal of treatment

- Control of symptoms
- Prolongation of life
- Good quality of life
### Individualized Treatment Selection

<table>
<thead>
<tr>
<th>Triple negative ER- and PR- HER2-</th>
<th>HER positive HER2+</th>
<th>Hormone positive ER+ and/or PR+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ET responsive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ET non-responsive (ET refractory, short DFI, rapid growing visceral mets)</td>
</tr>
</tbody>
</table>

- **Anti-HER2**
- **Endocrine therapy**
- **Chemotherapy**

CT still remains important treatment option for a vast majority of ABC patients!
NCCN Guidelines Version 2.2015
Invasive Breast Cancer

CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER

Preferred single agents:
- Anthracyclines
  - Doxorubicin
  - Pegylated liposomal doxorubicin
- Taxanes
  - Paclitaxel
- Anti-metabolites
  - Capecitabine
  - Gemcitabine
- Other microtubule inhibitors
  - Vinorelbine
  - Eribulin

Other single agents:
- Cyclophosphamide
- Carboplatin
- Docetaxel
- Albumin-bound paclitaxel
- Cisplatin
- Epirubicin
- Ixabepilone

Chemotherapy combinations:
- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab

Preferred first-line agents for HER2-positive disease:
- Pertuzumab + trastuzumab + docetaxel (category 1)
- Pertuzumab + trastuzumab + paclitaxel

Other first-line agents for HER2-positive disease:
- Trastuzumab alone or with:
  - Paclitaxel ± carboplatin
  - Docetaxel
  - Vinorelbine
  - Capecitabine

Preferred agents for trastuzumab-exposed HER2-positive disease:
- Ado-trastuzumab emtansine (T-DM1)

Other agents for trastuzumab-exposed HER2-positive disease:
- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents
Optimal use of chemotherapy in mBC?

- Combination HT or sequential use of single agents?
- Optimal duration of chemotherapy?

Options available

- “Old” agent recycled (capecitabine, liposomal anthracyclines, nab-paclitaxel, platinum derivatives in TNBC)
- “New” cytotoxic agents targeting microtubules (Eribulin, Epothilones)
- Rechallenge
  - Re-usage of taxanes might be considered in pts with DFI longer than 1 year\(^1\)
- Decision on which drug should be individualized and take into account previous exposure, patient preference and country availability\(^2\)

Palmieri et al., Nat Rev Clin Oncol 2010
## Efficacy data from randomized Studies in monotherapy Arm

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Comparison (x number of cycles)</th>
<th>Number of patients</th>
<th>Response Rate (%)</th>
<th>Time to Progression (months)</th>
<th>Overall Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alba</td>
<td>2004</td>
<td>A x 3 → Doc x 3 A + Doc x 6</td>
<td>144</td>
<td>61</td>
<td>10.5</td>
<td>22.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>51</td>
<td>9.2</td>
<td>21.8</td>
</tr>
<tr>
<td>Beslija</td>
<td>2006</td>
<td>Doc → X Doc + X</td>
<td>100</td>
<td>40</td>
<td>7.7</td>
<td>19.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>68*</td>
<td>9.3*</td>
<td>22.0*</td>
</tr>
<tr>
<td>Conte</td>
<td>2004</td>
<td>E x 4 → Pac x 4 E + Pac x 8</td>
<td>202</td>
<td>58</td>
<td>10.8</td>
<td>26.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>58</td>
<td>11.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Koroleva</td>
<td>2001</td>
<td>Doc x 4 → A x 4 A + Doc x 8 A + Doc x 8</td>
<td>193</td>
<td>56</td>
<td>6.9</td>
<td>13.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>49</td>
<td>6.7</td>
<td>11.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>59</td>
<td>8.3</td>
<td>14.5</td>
</tr>
<tr>
<td>Sjöstrom</td>
<td>1999</td>
<td>Doc MF</td>
<td>238</td>
<td>42*</td>
<td>6.3*</td>
<td>10.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21</td>
<td>3.0</td>
<td>11.1</td>
</tr>
<tr>
<td>Sledge</td>
<td>2003</td>
<td>A Pac A + Pac</td>
<td>739</td>
<td>36</td>
<td>5.8</td>
<td>18.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>34</td>
<td>6.0</td>
<td>22.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>47*</td>
<td>8.0*</td>
<td>22.0</td>
</tr>
<tr>
<td>Soto</td>
<td>2006</td>
<td>X → Pac or Doc X + Pac X + Doc</td>
<td>368</td>
<td>45</td>
<td>8.4</td>
<td>31.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>64*</td>
<td>6.7</td>
<td>33.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>75*</td>
<td>8.1</td>
<td>28.5</td>
</tr>
<tr>
<td>Tomova</td>
<td>2008</td>
<td>Doc x 4 → G x 4 Doc + G x 8</td>
<td>100</td>
<td>28</td>
<td>6.7</td>
<td>15.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>31</td>
<td>7.0</td>
<td>15.5</td>
</tr>
</tbody>
</table>

Grade ≥3- febrile neutropenia, mucositis, diarrhea, neurotoxicity

* $p \leq .05$
Combination chemotherapy vs. sequential use of single agents?

- Most trials and meta-analysis compare single agent vs. combination and NOT sequential use of single agents vs. combination HT
- Cochrane Review (28 studies, 5707 pts) – combination HT was associated with higher RR, TTP (HR= 0.78, p < .001), and longer OS (HR 0.88, p < .001)

More toxicity – nausea, vomiting, leucopenia and alopecia

**COMBINATION**
- Higher RR
- Faster symptom/disease control
- Higher toxicity

**SEQUENTIAL USE OF SINGLE AGENTS**
- Lower Toxicity
- Slower symptom/disease control
- Better management of resources

**SIMILAR SURVIVAL!!!**

**Life-threatening, rapid clinical progression and/or highly symptomatic (and/or young pts)**

**Non-life-threatening and/or oligo-symptomatic (and/or elderly)**

**Optimal duration of chemotherapy?**

- **Progression free survival**
  - Longer HT duration:
    - significant and clinically meaningful improvement in PFS (HR 0.64; 95% CI 0.55 – 0.76)
    - significant improvement in OS (HR 0.91; 95% CI 0.84-0.99)

---

**Overall survival**

- **Gennari A, et al. JCO 2011;29:2144-2149**
``New`` cytotoxic agent- ERIBULIN

- EMBRACE: Eribulin in Heavily Pre-treated pts (2-5 prior cht)

**Eribulin vs. Capecitabine in Previously Treated MBC**

- Similar overall activity
- 1st drug to “as good as capecitabine” in 1st/2nd line
- New good treatment option


Retrospective Analysis of nab-Paclitaxel as First-Line Therapy for MBC with Poor Prognostic Factor

- **Study CA012**: Compared with 3-weekly paclitaxel- Higher RR, Higher TTP and slightly better OS\(^1\)

- **Study CA024**: Compared with docetaxel- Better RR and PFS, specially the weekly (150 mg) regimen\(^2\)

- Median OS longer with 150 mg/m\(^2\) qw compared with docetaxel but not statistically significant\(^3\)

- Different toxicity profile

The results suggest superiority of nab-paclitaxel q3w compared with other taxanes and of nab-paclitaxel qw compared with q3w are retained in patients who are difficult to treat due to poor prognostic features

Impact of BRCA1/2 Mutation Status on Response to Platinum-Based Chemotherapy in Triple-Negative Breast Cancer in the TBCRC009 Trial

<table>
<thead>
<tr>
<th></th>
<th>All Patients n=86</th>
<th>BRCA1/2 Positive n=11</th>
<th>BRCA1/2 WT n=65</th>
<th>Unknown n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>30.2%</td>
<td>54.6%*</td>
<td>26.2%</td>
<td>30%</td>
</tr>
<tr>
<td>Median PFS</td>
<td>88 days</td>
<td>96 days</td>
<td>86 days</td>
<td>--</td>
</tr>
</tbody>
</table>

* P=.079 versus BRCA1/2 WT

- 6 patients (7%) are long-term survivors who achieved durable responses and remain off all therapy (median 4.5 years); all of these patients are BRCA1/2 WT (5) or unknown (1), and received platinum therapy as first-line treatment for MBC
Anti HER 2 therapy

• Anti HER 2 therapy should be offered early to all HER2+ patients
• The choice of anti HER2 agents will depend on therapy previously administrated, relapse free interval and country-specific availability
• It is important to keep blocking the HER2 pathway after progression on anti HER2 therapy!!!
• The optimal sequence of all available anti HER2 therapies is currently unknown.

What is new promising results for mBC in the last few years?

Milestones of anti-HER2 therapies in MBC

1998
FDA approved trastuzumab alone for 2nd line and in with paclitaxel for 1st line MBC

2007
FDA approved lapatinib + capecitabine for MBC

2010
FDA approved lapatinib + letrozole for MBC

2012
FDA approved pertuzumab + trastuzumab + docetaxel for MBC

2013
FDA approved trastuzumab emtansine for MBC

MBC: metastatic breast cancer; MoAb: monoclonal antibody
Prognosis of Women With Metastatic Breast Cancer by HER2 Status and Trastuzumab Treatment: An Institutional-Based Review

Shaheenah Dawood, Kristine Broglio, Aman U. Buzdar, Gabriel N. Hortobagyi, and Sharon H. Giordano

Overall survival by trastuzumab treatment group

- HER2/neu negative
- No trastuzumab
- Trastuzumab

No. of patients at risk:

<table>
<thead>
<tr>
<th>Status</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2/neu negative</td>
<td>1,782</td>
<td>1,060</td>
<td>633</td>
<td>348</td>
<td>211</td>
<td>120</td>
</tr>
<tr>
<td>No trastuzumab</td>
<td>118</td>
<td>65</td>
<td>31</td>
<td>16</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>191</td>
<td>155</td>
<td>94</td>
<td>51</td>
<td>25</td>
<td>10</td>
</tr>
</tbody>
</table>
CLEOPATRA


…for the 1st line
Lapatinib in Trastuzumab-refractory mBC

- Lapatinib ↑ TTP (HR 0.49, P<.001)
- No significant OS difference

OS
- Lap+Cap 75 weeks
- Cap 64.7 weeks
- HR 0.87; p= .21

...for the 2nd line

Cameron D, et al. Oncologist 2010
EMILIA
Phase III registration trial

...for the 2nd line

THERESSA
Randomised, phase 3 trial

...and beyond

**Reccomendation**

**First line**
- Pertuzumab + Trastuzumab + Docetaxel
- Pertuzumab + Trastuzumab + Paclitaxel
- Trastuzumab emtansine (relaps 6 months after or during adj. trastuzumab)
- AI + Trastuzumab or Lapatinib (HR +/-HER2 + BC)

**Second line**
- Trastuzumab emtansine
- Lapatinib + Capecitabine
- Trastuzumab + Capecitabine/other agents
- Trastuzumab + Lapatinib
- Pertuzumab + Trastuzumab + Taxanes

**Third+ line**
- Trastuzumab emtansine
- Lapatinib + Capecitabine
- Trastuzumab + Lapatinib
- Trastuzumab + chemotherapy (treatment after progression)

Endocrine therapy in mBC

- Endocrine therapy (ET) is the preferred option for HR+ disease, even in the presence of visceral disease, unless there is concern or proof of endocrine resistance or rapidly progressive disease needing a fast response.

- How to enhance sensitivity to endocrine therapy? PI3K/AKT/mTOR Inhibition in HR+ Advanced BC

- Dual blockade of the mTOR and endocrine pathways via mTOR inhibition in combination with endocrine therapy offers clinical benefits for patients progressing on NSAIIs.

- Overcoming resistance → prolong PFS, OS
- After NSAI Fulvestrant HD is alternative option!
BOLERO 2

Median follow up 18 months

OS events
Everolimus vs. placebo
25.4% vs. 32.2%
Δ OS events
6.8%

Possible algorithm for ER+/HER 2- ABC progressing on prior NSAI

Endocrine therapy (ET) treatment guidelines for postmenopausal patients with hormone receptor–positive and human epidermal growth factor receptor 2–negative advanced breast cancer recurring or progressing on prior nonsteroidal aromatase inhibitor therapy.

a For patients 70 years of age or older, or for those with multiple comorbidities or frailties compromising overall health status, consideration should be given to a reduced starting dose of 5 mg daily, followed by potential dose escalation based on tolerance. EVE = everolimus; EXE = exemestane; F500 = fulvestrant 500 mg; F250 = fulvestrant 250 mg; CT = chemotherapy.

Role of antiangiogenic agents in the 1\textsuperscript{st} line of mBC

Meta-analysis of 1\textsuperscript{st} line phase III studies - 2695 pts

30\% risk reduction of PFS event (HR 0.70, 95\%CI 0.57-0.86)
No OS benefit (HR 0.95, 95\%CI 0.85-1.06)

IMELDA: In patients benefiting from first-line BEV containing therapy, continued BEV with oral chemotherapy (Capecitabine) improves efficacy (HR 0.38, p<.001, 11.9 vs. 4.3 months)\(^1\)

Statistically significant improvement in second-line PFS with further BEV in BEV-pretreated LR/mBC (TANIA)\(^2\)

Effect of second-line BEV on PFS in BEV-pretreated patients (TANIA) appears similar to effect in BEV-naïve patients (RIBBON-2; HR 0.78 [95%CI0.64–0.93])\(^3\)

Metronomic Chemotherapy
``chronic`` low dose chemotherapy for `` chronic``disease

• Metronomic chemotherapy generally refers to repetitive, low doses of chemotherapy drugs administered at close intervals with no extended interruption

• Targets the tumor microenvironment in addition to tumor cells

✓ Low-dose schedule compromises the repair process of endothelial cells, leading to an antiangiogenic effect

Benefits of Metronomic Chemotherapy

• Attractive to consider a therapeutic strategy with good toxicity profile
• Good tumor control
• Not expensive for the health system

What Are the Ideal Agents to Use for Metronomic Dosing?

• Oral chemotherapeutic agents
  – Well-tolerated
  – Inexpensive
• Lack of cumulative toxicity important
Clinical Benefit (CB) With Metronomic Chemotherapy in Advanced Breast Cancer

**FIRST STUDY**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>DAY</th>
</tr>
</thead>
<tbody>
<tr>
<td>methotrexate</td>
<td>2,5 mg X 2 oral</td>
<td>1</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>50 mg oral</td>
<td>2,3,4,5,6,7</td>
</tr>
</tbody>
</table>

CB 31.7%

**SECOND STUDY**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>DAY</th>
</tr>
</thead>
<tbody>
<tr>
<td>methotrexate</td>
<td>2,5 mg X 2 oral</td>
<td>1</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>50 mg oral</td>
<td>2,3,4,5,6,7</td>
</tr>
</tbody>
</table>

CB 41.5%

### Metronomic CT in Pretreated Patients

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>N Patients</th>
<th>Treatment</th>
<th>Phase</th>
<th>ORR, %</th>
<th>CB %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colleoni 2002</td>
<td>63</td>
<td>Cyclophosphamide Methotrexate</td>
<td>II</td>
<td>19</td>
<td>39.7</td>
</tr>
<tr>
<td>Colleoni 2005</td>
<td>171</td>
<td>Cyclophosphamide Methotrexate</td>
<td>Rand</td>
<td>20.9 vs 41.5</td>
<td>41.5 vs 41.5</td>
</tr>
<tr>
<td>Orlando 2006</td>
<td>22</td>
<td>Cyclophosphamide Methotrexate Thalidomide</td>
<td>II</td>
<td>18</td>
<td>46</td>
</tr>
<tr>
<td>Dellapasqua 2008</td>
<td>46</td>
<td>Cyclophosphamide Capecitabine Bevacisumab</td>
<td>II</td>
<td>48</td>
<td>68</td>
</tr>
<tr>
<td>Garcia-Saenz 2008</td>
<td>24</td>
<td>Cyclophosphamide Capecitabine Bevacisumab</td>
<td>II</td>
<td>31.8</td>
<td>63.6</td>
</tr>
<tr>
<td>Wang 2012</td>
<td>68</td>
<td>Cyclophosphamide Capecitabine</td>
<td>II</td>
<td>30.3</td>
<td>53</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>N Patients</th>
<th>Treatment</th>
<th>Phase</th>
<th>ORR, %</th>
<th>CB %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fedele 2012</td>
<td>60</td>
<td>Capecitabine</td>
<td>II</td>
<td>24</td>
<td>62</td>
</tr>
<tr>
<td>Saridaki 2012</td>
<td>36</td>
<td>Vinorelbine, Capecitabine</td>
<td>I</td>
<td>46</td>
<td>/</td>
</tr>
<tr>
<td>Yoshimoto 2012</td>
<td>51</td>
<td>Capecitabine, Cyclophosphamide</td>
<td>II</td>
<td>44</td>
<td>57.8</td>
</tr>
<tr>
<td>Young 2012</td>
<td>47</td>
<td>Docetaxel, Capecitabine, Celecoxib</td>
<td>II</td>
<td>34</td>
<td>42</td>
</tr>
<tr>
<td>Mayer 2012</td>
<td>23</td>
<td>Cyclophosphamide, Methotrexate, Vandetanib</td>
<td>I</td>
<td>(10)</td>
<td>(25)</td>
</tr>
<tr>
<td>Otsuka 2013</td>
<td>40</td>
<td>Irinotecan, Tegafur</td>
<td>II</td>
<td>47</td>
<td>/</td>
</tr>
<tr>
<td>Schwartzberg 2013</td>
<td>41</td>
<td>Capecitabine, Fulvestrant</td>
<td>II</td>
<td>24.4</td>
<td>58.1</td>
</tr>
<tr>
<td>Cazzaniga 2014</td>
<td>12+22</td>
<td>Capecitabine, Vinorelbine, Fulvestrant</td>
<td>I-II</td>
<td>58</td>
<td></td>
</tr>
</tbody>
</table>

• Metronomic chemotherapy has additional effects on endothelial cells and immune function

• Provides disease control for a significant proportion of patients

• Increased attention to patients' quality of life favors the use of active oral treatments

• Combinations with targeted therapeutics-Increased costs, increased toxicity and increased complexity (eg. iv drugs)

• The low burden of personal costs to the patient and the possibility to continue the treatment for several months support the use of metronomic CT as an additional therapeutic tool
``It ain't over 'til it's over``

Palliative care

Sometimes “active treatment” goals are unrealistic
Drop the goal ``prolongation of life``
Focus only on “comfort care”
• Relieve pain and other symptoms
• Quality of life for both the patient and the family
• Emotional and spiritual concerns
• May be best served by hospice
Future direction

• Next generation sequencing
• Personalized medicine