Chemotherapy-Endocrine Therapy Sequence in Premenopausal Patients

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Chemotherapy-Endocrine Therapy Sequence in Premenopausal Patients

- No reference
- The most challenging topic
- Based on individual clinical experiences
- Half & Half epidemiology in Asia
ENDOCRINE THERAPY IS THE OLDEST TARGETED THERAPY IN BREAST CANCER

Estrogen

Target tissues:
- Breast tissue
- Peripheral tissue
- Tumor tissue

Estrogen-receptor

DNA

Proliferation

Angiogenesis
**NCCN Guidelines Version 2.2017**

**Invasive Breast Cancer**

**SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE**

ER and/or PR POSITIVE; HER2 NEGATIVE OR POSITIVE

- **Premenopausal**
  - Prior endocrine therapy within 1 y
  - Postmenopausal

- **Visceral crisis**
  - Consider initial chemotherapy (See BINV-21 and BINV-22)

ER and/or PR positive; HER2 negative

- **Premenopausal**
  - Ovarian ablation or suppression, plus endocrine therapy as for postmenopausal women

ER and/or PR positive; HER2 positive

- **Premenopausal**
  - Aromatase inhibitor or selective ER modulators or selective ER down-regulator
  - Palbociclib + letrozole (category 1)
  - Ribociclib + letrozole (category 1)

- **Postmenopausal**
  - Consider initial chemotherapy (See BINV-21 and BINV-22)
Endocrine therapy (ET) is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is concern or proof of endocrine resistance, or there is disease needing a fast response (LoE: 1 A).

Total number of votes: 29
1. YES: 100% (29)
2. NO: 0%
3. ABSTAIN: 0%
ABC important definitions

- **Visceral crisis** is defined as *severe organ dysfunction* as assessed by signs and symptoms, laboratory studies, and *rapid progression of disease*.

- **Visceral crisis** is not the mere presence of visceral metastases but implies important visceral compromise leading to a clinical indication for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible.

- **Primary endocrine resistance** is defined as: Relapse while on the first 2 years of adjuvant ET, or PD within first 6 months of 1st line ET for MBC, while on ET.

- **Secondary (acquired) endocrine resistance** is defined as: Relapse while on adjuvant ET but after the first 2 years, or relapse within 12 months of completing adjuvant ET, or PD ≥ 6 months after initiating ET for MBC, while on ET.
Points of transition from endocrine to chemotherapy

Metastatic breast cancer – SABCS 2014
Visceral metastases from hormone receptor positive BC as sensitive to endocrine therapy as non-visceral metastasis - P1-13-02

Figure 2. Kaplan-Meier plot of DoCB in patients with visceral metastases versus non-visceral metastases (combined tamoxifen arms from all trials)

Figure 3. Kaplan-Meier plot of DoCB in patients with visceral metastases versus non-visceral metastases (all endocrine therapies combined from all trials)

Robertson JFR et al. SABCS 2014 – P1-13-02
Therapy strategy in MBC

**Symptoms / Metastasis location**
- **Slow disease progression**
  - Steroid hormone receptor status (ER, PR)
    - ER / PR positive
      - Endocrine therapy
        - Exemestane + Everolimus
    - ER and PR negative
      - HER2 status
        - HER2 positive: + trastuzumab + pertuzumab / T-DM1 / lapatinib
        - HER2 negative: ± bevacizumab

**Rapid therapy response required**
- Bone metastases: + bisphosphonates / denosumab

Depending on clinical situation (response, disease progression)

Modified after Bossung & Harbeck, Curr Opin Obs&Gyn '10
Current ESMO Guidelines for the use of first-line endocrine therapy in postmenopausal ER+ MBC

ET, endocrine therapy; CT, chemotherapy; HER2, HER2-directed therapy; T, trastuzumab.
Endocrine therapy for MBC: Standards

- Endocrine therapy is the therapeutic backbone in early and advanced hormone receptor positive breast cancer
- Current guidelines support continuing endocrine-based therapeutic approaches after HR+ ABC progresses
- Options for post-progression ET
  - Switching to a different ET
  - Combining ET agents does not appear to add benefit; increasing dose intensity might provide benefit
  - **Adding a targeted agent to ET is a new standard option**
Original article

Chemotherapy versus endocrine therapy as first-line treatment in patients with luminal-like HER2-negative metastatic breast cancer: A propensity score analysis

Marta Bonotto a,b,*, Lorenzo Gerratana a,b, Massimo Di Maio c, Carmine De Angelis d, Marika Cinausero a,b, Stefano Moroso b, Monica Milano d, Brigida Stanzione d, Piera Gargiulo d, Donatella Iacono b, Alessandro Marco Minisini b, Mauro Mansutti b, Gianpiero Fasola b, Sabino De Placido d, Grazia Arpino d, Fabio Puglisi a,b

a Department of Medical and Biological Sciences, University of Udine, Udine, Italy
b Department of Oncology, University Hospital of Udine, Udine, Italy
c Department of Oncology, San Luigi Gonzaga Hospital, Orbassano (TO), Italy
d Department of Clinical Medicine and Surgery, University of Naples Federico II, Italy
Description of therapeutic strategy
(CT, chemotherapy; ET, endocrine therapy)

- **171 (38%)** received first-line CT.

- The only factors significantly associated with lower CT use were *old age* (OR 0.25, 95%C.I. 0.13-0.49) or *presence of bone metastases only* (OR 0.26, 95%C.I. 0.13-0.53).

- The choice was mainly driven by *age* and *site of metastases*.
Original article

Disease management patterns for postmenopausal women in Europe with hormone-receptor-positive, human epidermal growth factor receptor-2 negative advanced breast cancer
Physician-reported reasons of choice for endocrine versus chemotherapy

“Absence of life-threatening metastasis” and “slow disease progression” are the major drivers of choice for first-line endocrine therapy.
Real-world patterns of use of chemotherapy vs. endocrine therapy (n=355, 5 European countries)

Cohort (First – third line)

A
62% of patients
(n = 218)

First-line therapies
ET ± TT
(n = 218)
39 weeks
Second-line therapies
CT ± HT ± TT
(n = 218)
24 weeks
Third-line therapies
Any (or none)
(n = 69 Tx, 149 none)
28 weeks

B
7% of patients
(n = 26)

ET ± TT
(n = 26)
46 weeks
ET ± TT
(n = 26)
31 weeks
CT ± HT ± TT
(n = 26)
23 weeks

C
31% of patients
(n = 111)

CT ± HT ± TT
(n = 111)
28 weeks
Any therapy
(n = 111)
34 weeks
Any (or none)
(n = 38 Tx, 73 none)
25 weeks

Majority (69%) of patients received HT in the first-line setting

What about premenopausal diseases?
The role of chemotherapy in premenopausal women with ER-positive and HER2-negative MBC

- 50% of the patients (135/272) received first-line chemotherapy.
- Among them, 42% of the patients (57/135) could receive chemotherapy followed by maintenance sequential endocrine therapy without progression.
- The remaining 58% of the patients (78/135) received 2nd line chemotherapy because of early progression.

In submission
Patients’ characteristics of SMC premenopausal cohort

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (N = 272)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>39 (16-50)</td>
</tr>
<tr>
<td>ECOG (N = 191)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>88 (46.1%)</td>
</tr>
<tr>
<td>1</td>
<td>100 (52.4%)</td>
</tr>
<tr>
<td>2</td>
<td>3 (1.6%)</td>
</tr>
<tr>
<td>Disease status</td>
<td></td>
</tr>
<tr>
<td>De novo</td>
<td>89 (32.7%)</td>
</tr>
<tr>
<td>Recurred</td>
<td>183 (67.3%)</td>
</tr>
<tr>
<td>Disease-free interval in recurred pop.</td>
<td></td>
</tr>
<tr>
<td>&gt; 12 months from adjuvant Tx to recurrence</td>
<td>48 (27.3%)</td>
</tr>
<tr>
<td>≤ 12 months from adjuvant Tx to recurrence</td>
<td>128 (72.7%)</td>
</tr>
<tr>
<td>Disease site</td>
<td></td>
</tr>
<tr>
<td>Symptomatic visceral</td>
<td>63 (23.2%)</td>
</tr>
<tr>
<td>Asymptomatic visceral</td>
<td>69 (25.4%)</td>
</tr>
<tr>
<td>Bone and soft tissue only</td>
<td>140 (51.4%)</td>
</tr>
<tr>
<td>Receptor status</td>
<td></td>
</tr>
<tr>
<td>ER+ and PgR+</td>
<td>231 (84.9%)</td>
</tr>
<tr>
<td>ER+ and PgR-</td>
<td>34 (12.5%)</td>
</tr>
<tr>
<td>ER- and PgR+</td>
<td>7 (2.6%)</td>
</tr>
</tbody>
</table>

ABC guideline

- **Endocrine treatment after CT** *(maintenance ET)* to maintain benefit is a reasonable option, although this approach has not been assessed in randomized trials.

42% among the patient who received first-line CT could receive CT followed by maintenance sequential ET without progression.
Why Premenopausal in Asia?

Western

- Pre: 15%
- Post: 85%

Asia

- Pre: 50%
- Post: 50%

Premenopausal BC: 50%
- China, India, Korea, Taiwan, Japan
Figure 4

Trends in the median age at breast cancer diagnosis in Korea, and the ratio of postmenopausal to premenopausal women at diagnosis.

Source: Kim et al
Case 1 (F/43)

- 2016.04.27. diagnosed as invasive ductal carcinoma of breast with lung, pleura, mediastinal LNs, and multiple bone metastases

Breast, right upper outer quadrant, core biopsy:
- **INVASIVE CARCINOMA** with lobular feature
- No microcalcification

<< Result of immunohistochemical staining
- Estrogen receptor: Positive (> 2/3)
- [IS(3)+PS(5)=TS(8)]
  - Internal control: present (positive)
- Progesterone receptor: Positive (> 2/3)
- [IS(3)+PS(5)=TS(8)]
  - Internal control: present (positive)
- HER2: Negative (0)
- Ki-67: Positive (1+, 5-10%)

**Higher tumor burden without visceral crisis cc)** Back pain d/t L1 metastases without pathologic compression fracture

- Goserelin + Tamoxifen start at 2016.05.13
- RTx to L-spine & pelvic bone from 2016.05.19 to 2016.06.07. with zoledronic acid
- Regular menstruation

- Revisit at 2016.07.07. with dyspnea and severe multiple bone pain
- Progression on multiple lung & pleura
- Switch to AC at 2016.07.08
Case 1 (F/43)

- 2016.07.08-2016.12.02. AC #8 (ADR cumulative dose 420 mg/m²)

- Resume to tamoxifen at 2017.01.13 till now
Case 2 (F/37)

- 2008.10.15.-2009.04.02 Neoadjuvant AC #4 + Paclitaxel #4
- 2009.05.03. right MRM with ALND ypT1c(1.8cm)N1(1/13) Invasive ductal carcinoma, ER+/PR+/HER2-
- GNRH agonist + Tamoxifen for 2 years
- ~Tamoxifen till 2012.07.25
- Progression on bone & multiple LNs

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<tr>
<td>p53 protein:</td>
<td>Negative (&lt;5% of tumor cells)</td>
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<td>HER2:</td>
<td>Negative (1+)</td>
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<tr>
<td>Ki-67:</td>
<td>Positive (1+)</td>
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<tr>
<td>CK5/6:</td>
<td>Negative</td>
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<td>EGFR:</td>
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- 2012.08.05-2012.12.16. Goserelin + Anastrozole
- 2012.12.21-2014.04.15. Capecitabine #21
- 2014.05.12. Bilateral oophorectomy for surgical ovarian ablation
Case 2 (F/37)

- 2014.06.01.-2014.09.11. Fulvestrant #3
- Progression on pericardium & lymphangitic lung metastases
- 2014.10.02-2016.03.09. Paclitaxel + Gemcitabine #22
- Progression on pericardium & mediastinal LNs
- 2016.04.11. pericardial window formation d/t cardiac tamponade

![Result of immunohistochemical staining (Estrogen receptor, pericardium)](image)

- 2016.04.30-2016.06.15. exemestane + everolimus
- Progression on mediastinal LNs, lung, and liver
- 2016.06.20-2017.02.23. eribulin #12
Case 2 (F/37)

- 2008.10.15.-2009.04.02 Neoadjuvant AC #4 + Paclitaxel #4
- 2009.05.03. right MRM with ALND ypT1c(1.8cm)N1(1/13)
  Invasive ductal carcinoma, ER+/PR+/HER2-
- GNRH agonist + Tamoxifen for 2 years
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- 2012.08.05-2012.12.16. Goserelin + Anastrozole  **PFS 4.0 months**
- 2012.12.21-2014.04.15. Capecitabine #21
- 2014.05.12. Bilateral oophorectomy for surgical ovarian ablation
Case 2 (F/37) - postmenopausal state

- 2014.06.15.-2014.09.11. Fulvestrant #3  **PFS 3 months**
- Progression on pericardium & lymphangitic lung metastases
- 2014.10.02-2016.03.09. Paclitaxel + Gemcitabine #22
- Progression on pericardium & mediastinal LNs
- 2016.04.11. pericardial window formation due to cardiac tamponade
- **Primary Endocrine Resistance**

Pericardium, pericardial window formation:

<table>
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<th>Metastatic ductal adenocarcinoma</th>
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<tbody>
<tr>
<td>Estrogen receptor: Positive (&gt; 2/3)</td>
</tr>
<tr>
<td>[1S(3)+PS(5)=TS(8)] Internal control: not present</td>
</tr>
<tr>
<td>Progesterone receptor: Negative (No staining)</td>
</tr>
<tr>
<td>[1S(0)+PS(0)=TS(0)] Internal control: not present</td>
</tr>
<tr>
<td>HER2: Negative (1+)</td>
</tr>
</tbody>
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- 2016.04.30-2016.06.15. exemestane + everolimus  **PFS 2 months**
- Progression on mediastinal LNs, lung, and liver
- 2016.06.20-2017.02.23. eribulin #12
Study Design

Prospective, phase III, multi-center, randomized study
Enroll period: 2007.05 – 2010.09

324 MBC patients with no prior chemotherapy

6 cycles of PG

PG regimen
Paclitaxel 175 mg/m² Day 1
Gemcitabine 1,250 mg/m² Day 1 & 8 every 3 weeks

Primary Objective: PFS from Randomization
Secondary Objectives: OS, Toxicities, QoL, and Response Duration

Notably, the benefits of continued therapy seem most marked in younger, premenopausal patients, those with CR/PR as opposed to SD after GT x 6, and to a lesser extent, patients with visceral disease, hormone receptor negative disease, and a larger number of disease sites.
Experience from PG maintenance trial

• The fact that hormonal therapy was not allowed after randomization and before disease progression suggests that patients entering this trial largely have hormone-refractory disease.

• It is therefore hard to understand why, with about three-quarters of patients having hormone-positive disease, 98% with ECOG PS 0–1, only about 20% of patients received palliative hormonal therapy for metastatic disease before enrollment in this first-line chemotherapy trial.

• Approximately half of the patients were premenopausal and young, which is supported that the peak age in Asia-Pacific area including Korea is much younger than that in western countries.

• More than 40% of the patients had received adjuvant endocrine therapy already.

• About 65% of the patients had visceral diseases (lymphangitic pulmonary metastases and/or hepatic metastases).

• Two third of the patients had 2 or more metastatic sites.
Maintenance therapy in breast cancer—many questions remain

Miguel Martín and Sara López-Tarruella

A recent clinical trial showed that a significant progression-free and overall survival benefit was associated with maintenance chemotherapy in patients with HER2-negative metastatic breast cancer who have disease control after six cycles of conventional chemotherapy. However, the choice of observation alone as the control arm limits the clinical application of these data.


The Search for an Elusive Uniform Strategy for a Heterogeneous Disease: Lesson Learned?

Andrew D. Seidman, Breast Cancer Medicine Service, Memorial Sloan-Kettering Cancer Center; Weill Cornell Medical College, New York, NY

See accompanying article on page 1732
Asian premenopausal BC may have distinctive biologic feature?

Figure 4. Landscape of somatic alterations in SMC and TCGA cohorts

Heatmap showing protein-altering somatic mutations and copy number alterations affecting 18 most frequently altered genes, \( \geq 10\% \) in the combined SMC and TCGA cohorts and \( \geq 5\% \) of the SMC cohort. Genes are ranked by alteration prevalence in descending order. Only functional alterations classified based on a knowledgebase matching approach were considered. We found that TP53 (SMC: 48\% vs. TCGA: 28\%), ERBB2 (22\% vs 10\%), AKT1 (2.7\% vs 0.3\%) and GATA3 (13\% vs 7\%) alterations are significantly enriched in the Korean BCs while CDH1 alterations (4\% vs 10\%) are significantly enriched in the American cohort (FDR < 0.2).

Chemotherapy-Endocrine Therapy Sequence in Premenopausal Patients.....

- **Is still open clinical question.**
  - Is ET standard also true in Asian population including Korea?
  - Real world situation in Asia (premenopausal 50% vs. postmenopausal 50%)
  - Who should be selected for the first-line chemotherapy than endocrine therapy?
  - Chemotherapy followed by endocrine therapy could be a therapeutic option?
  - Role of endocrine therapy combined new targeted therapy in premenopausal women should be defined further.
Thank You!

THANK YOU FOR YOUR ATTENTION!