ESMO PRECEPTORSHIP ON BREAST CANCER

Chemotherapy for early stage ER+ Breast Cancer

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DISCLOSURE OF INTEREST

- Medical oncologist
- Private practise
- Johannesburg

- No conflicts of interest
- No financial relationships relevant to this presentation
Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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For the purpose of the ESMO guidelines, inoperable locally advanced breast cancer is considered part of advanced breast cancer (ABC) and is discussed in the ABC guidelines; it will not be addressed in this present manuscript.
LEARNING OBJECTIVES

- General principles
  - Management
- Treatment algorithms
  - Chemotherapy
  - Intrinsic subtypes
- (Neo) adjuvant chemotherapy
  - Treatment principles
  - Special populations
- Personalised medicine
  - Gene signatures
TREATMENT

General Recommendations

- Specialised Breast Centres
- High volume unit (>150 new cases per year)
- Better outcomes in DFS, OS & QOL
- Certified/Accredited
- Medical oncologists
- Breast surgeons
- Radiation oncologists
- Breast radiologists
- Breast pathologists
- Breast nurses

Cardoso et al, Euro J Cancer, 2017
- Patient information
- Involvement in decision making
- Diagnosis and treatment choices
- Verbally and writing
- Reliable information sources
TREATMENT DECISION MAKING

Consider

- Tumour burden and location
- Tumour biology
- Age
- General health status
- Patient preferences
- Younger patients
  - Fertility issues

Peccatori F, ESMO practice guidelines, Annals 2013
TREATMENT ALGORITHM
Marker expression & Intrinsic Subtype

Cardoso, F et al Annals:30, Jun 19
### SURROGATE DEFINITIONS OF INTRINSIC SUBTYPES OF BREAST CANCER

<table>
<thead>
<tr>
<th>Intrinsic Subtype</th>
<th>Clinicopathological Surrogate</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>ER+ Her2- Ki67 &lt;15% PR+</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>Low risk molecular signature</td>
<td></td>
</tr>
<tr>
<td>Luminal B</td>
<td>ER+ Her2- Ki67&gt;14% or PR -</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>High Risk molecular signature</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ER+ Her2+ any Ki67/PR</td>
<td></td>
</tr>
<tr>
<td>Her2</td>
<td>Her2 + ER- PR-</td>
<td>15 – 25%</td>
</tr>
<tr>
<td>Basal Like</td>
<td>TNBC</td>
<td>11 – 25%</td>
</tr>
</tbody>
</table>

Adapted from 2013 St Gallen Conference
CHEMOTHERAPY

- Adjuvant chemotherapy 3-6 weeks post surgery
- Neo-adjuvant chemotherapy at diagnosis once staging investigations have been completed
- Decision based on relapse risk vs cytotoxic benefit
- Remember to consider early and late therapy related toxicities
- Patients biological age, PS and preferences
- Luminal A with high tumour burden may be considered for chemotherapy
- Luminal B tumours more likely candidates
- May consider gene expression profiles
- Luminal B Her2+ usually get chemotherapy + anti her2 Rx + ET
- Chemotherapy not given concomitantly with ET
- If radiotherapy is also to be administered chemotherapy should be given first
ADJUVANT CHEMOTHERAPY (HR +)

- Absolute benefit biggest in ER- patients
- Regimens
  - Anthracyclines and Taxanes
  - CMF (lower risk patients)
  - TC (lower risk patients)
- No place for 6 cycles of 3 drug anthracycline-based regimen
- 5FU does not add benefit to anthracycline based regimens only toxicity (AC/EC)
- Platinum based compounds not routinely used in this setting
- Taxanes add to efficacy of adjuvant regimens
  - Sequentially better than concomitantly
  - Regimen maybe better if Taxanes initiated first?
- Anthracycline/taxane regimen reduces breast cancer mortality by 1/3
- Non anthracycline containing regimens are an alternative but shown to be inferior
PRIMARY SYSTEMIC THERAPY

- Large and locally advanced cancers
- Decrease extent of surgery
- In operable cases neo-adjuvant chemotherapy has no impact on survival
  - locoregional relapse rate
- Prognostic value and may guide post operative therapy
- Aim is to achieve pathological complete response (pCR)
- Lobular phenotype and Luminal A tumours are less sensitive to chemotherapy
- Drug selection is as for adjuvant therapy
- All cycles need to be given preoperatively to try and achieve pCR
(NEO)-ADJUVANT CHEMOTHERAPY IN HR+

Special populations

- Elderly patients
  - Adapted to biological age not chronological age
  - Consider less aggressive regimens in frail patients
  - Good PS patients should get standard regimens
  - Geriatric assessments prior to treatment decisions

- Male Breast Cancer
  - ET is SOC
  - Chemotherapy decisions as for female counterparts
PERSONALISED MEDICINE

- ER, PR, & Her2 predictive factors
- Surrogate intrinsic tumour phenotypes
  - based on biomarker expression
- uPA-PA11 used as a marker of tumour invasiveness
- Molecular signatures
  - Node negative / Her2 normal / 1-3 nodes
    - Oncotype Dx (TAILORx)$^1$
    - MammaPrint (Mindact)$^2$

1. Sparano et al, NEJM 2015/8
2. Cardoso et al, NEJM 2016
70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer

6693 Women with invasive early-stage breast cancer were enrolled

- 2634 Had low clinical risk and low genomic risk at enrollment
- 2745 Had low clinical risk and low genomic risk after correction

- 690 Had low clinical risk and high genomic risk at enrollment
- 592 Had low clinical risk and high genomic risk after correction

- 1497 Had high clinical risk and low genomic risk at enrollment
- 1550 Had high clinical risk and low genomic risk after correction
- 1873 Had high clinical risk and high genomic risk at enrollment
- 1806 Had high clinical risk and high genomic risk after correction

**Intention-to-Treat Population**
- 344 Were assigned to receive chemotherapy
- 346 Were not assigned to receive chemotherapy
- 690 Underwent randomization

- 4 Were ineligible
  - 57 Had a change in risk
  - 76 Did not receive chemotherapy
  - 5 Had unknown chemotherapy status

- 749 Were assigned to receive chemotherapy
- 748 Were not assigned to receive chemotherapy

- 11 Were ineligible
  - 26 Had a change in risk
  - 128 Did not receive chemotherapy
  - 9 Had unknown chemotherapy status

**Per-Protocol Population**
- 224 Were included in the per-protocol population
- 254 Were included in the per-protocol population
- 592 Were included in the per-protocol population
- 636 Were included in the per-protocol population

**Primary-test Population**
- 644 Were included in the primary-test population
- 21 Had a change in risk
- 85 Received chemotherapy
- 1 Had unknown chemotherapy status
MINDACT : NEJM AUG 2016
Clinical High Risk / Genomic Low Risk

- 58% > 2cm
- 93% G2/3
- 48% LN+ 1-3
- 98% HR+

- 5-year DMFS  94% (CI 92.5 – 96.2%)  
  no chemo 100% compliance
- Primary end point met : Non inferior 92% threshold met

94.7% 5-yr DMFS
P-value = 0.00939
MINDACT : NEJM AUG 2016
Clinical High Risk / Genomic Low Risk Chemo vs No Chemo

- No statistical difference
- 94% survival clinically high risk
MINDACT: CARDOSO, F NEJM AUG 2016

Enrollment
N = 6693

Clinical Risk = AdjuvantOnline
Clin-Low/MammaPrint Low
N = 2745
41%
No Chemotherapy
Endocrine Therapy

Clin-Low/MammaPrint High
N = 592
9%
Randomization
No CT
CT

Clin HIGH Risk
1 out of 2 discordant with Genomic Risk

Clin LOW Risk
1 out of 5 discordant with Genomic Risk

Genomic Risk = 70-gene MammaPrint signature
Clin-High/MammaPrint High
N = 1806
27%
Chemotherapy
Endocrine Therapy

No CT
CT

The goal of MINDACT:
To identify High Clinical Risk Patients who DO NOT benefit from chemotherapy
LOW CLINICAL HIGH GENOMIC RISK

- 9% total patients (592)
- 98% < 2cm
- 85% Grade 1/2
- 98% LN-
- 9% TNBC
- 12% Her-2+

- Randomized to chemotherapy / no chemotherapy
Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

TAILORx Methods: Treatment Assignment & Randomization
Accrued Between April 2006 - October 2010

Preregister - Oncotype DX RS (N=11,232) → Register (N=10,273)

ARM A: Low RS 0-10 (N=1629 evaluable)  
ASSIGN Endocrine Therapy (ET)

ARM B: Experimental Arm (N=3399)  
ET Alone

Mid-Range RS 11-25  
(N=6711 evaluable)

RANDOMIZE
Stratification Factors: Menopausal Status, Planned Chemotherapy, Planned Radiation, and RS 11-15, 16-20, 21-25

ARM C: Standard Arm (N=3312)  
ET + Chemo

ARM D: High RS 26-100  
(N=1389 evaluable)  
ASSIGN ET + Chemo
Recurrence Score® (RS) Result Increases

IDFS Decreases as

P<0.001

Arm A: ET alone (RS 0-10)
3% Distant recurrence rate

Arms B & C: Randomized (RS 11-25)
5% Distant recurrence rate overall

Arm D: Chemoendocrine (RS 26-100)
13% Distant recurrence rate despite chemotherapy + endocrine therapy

Joseph A. Sparano, MD

TAILORx Results

ITT Population: All Arms (A,B,C & D)

9-Year Event Rates
TAILORX RESULTS: SUMMARY

- Primary conclusions
  - RS 11-25: Endocrine therapy (ET) was non-inferior to chemotherapy + ET (primary endpoint - ITT)
  - RS 0-10: Distant recurrence rates very low (2-3%) with ET alone at 9 years
  - RS 26-100: Significantly higher event rates, driven by more recurrences despite adjuvant chemotherapy plus ET

- Other observations
  - Age – Recurrence Score® Result – Chemotherapy treatment interaction:
    - Some chemotherapy benefit in women 50 or younger with a RS 16-25
    - Greatest impact on distant recurrence with RS 21-25
PERSONALISED MEDICINE (GENE PROFILING)

- $T_{1-3}$ No Her2 normal Hormone receptor positive
  - Consider gene expression assay

- $T_x N_{1 \text{mic}} \leq 3 \text{ nodes}$ Her2 normal Hormone receptor positive
  - Consider gene expression assay
# GENE EXPRESSION PROFILING

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Method</th>
<th>Use</th>
<th>LoE</th>
<th>GoR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrinsic subtypes</td>
<td>Gene expression profile, N-Counter™ technology</td>
<td>Prognostic &lt;br&gt; Predictive: Different responses to neoadjuvant ChT and anti-HER2 therapy according to the subtype</td>
<td>II and III</td>
<td>B</td>
</tr>
<tr>
<td>First-generation signatures (Memora Print, Oncotype DX)</td>
<td>Gene expression profile, RT-PCR</td>
<td>For ER-positive, HER2-negative tumours &lt;br&gt; Prognostic &lt;br&gt; (Neo)Adjuvant ChT is indicated if high risk or high score &lt;br&gt; Can be carried out in biopsy or surgical specimen</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Second-generation signatures (Prosigna®, Endopredict®)</td>
<td>N-Counter™ technology, RT-PCR</td>
<td>For ER-positive, HER2-negative tumours; include T size and N status in their final score &lt;br&gt; Prognostic &lt;br&gt; (Neo)Adjuvant ChT is indicated if high risk or high score &lt;br&gt; Can be carried out in biopsy or surgical specimen</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

*A decrease in K667 expression during neoadjuvant ET is highly predictive of response.

ChT, chemotherapy; ER, oestrogen receptor; ET, endocrine therapy; GoR, grade of recommendation; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridisation; LoE, level of evidence; PgR, progesterone receptor; RT-PCR, reverse transcription polymerase chain reaction.
CONCLUSION

- Patients outcomes are best when managed within specialised breast units
- These outcomes are best achieved when patient care is undertaken within well established evidence-based treatment algorithms
- Specific clinicopathological criteria define those patients that benefit most from chemotherapy in the HR+ patient population
- Although there is no survival benefit for neo-adjuvant chemotherapy in operable breast cancer patients, this modality of therapy has a specific niche in the management of HR+ breast cancer
- The elderly patients need special consideration but if assessed as fit for cytotoxic therapy should be treated with standard chemotherapy protocols
- The incorporation of gene signature assays are becoming more common in early stage HR+ breast cancer and although these signatures may save many patients from the adverse effects of cytotoxic therapy, they also able to predict which patients could benefit from adjuvant systemic chemotherapy