Neoadjuvant Treatment of Breast Cancer

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Conflicts or Am I a Pharmaceutical Company Slut?

• Advisory Boards
  – Roche, GSK, sanofi aventis, Genetech, Array, Lilly, Novartis, AstraZeneca, Pfizer,

• Research Funding
  – Roche, GSK, AstraZeneca
Neoadjuvant Chemotherapy

- Systemic therapy given prior to surgery
  - Operable
  - Locally Advanced Breast Cancer (LABC)
  - Medically unstable patients
- Cytotoxic chemotherapy
- Hormonal therapy
  - Studies of AI vs Tamoxifen
- Presurgical/window studies
  - New agents, end point of tissue analysis
What are the indications for Neoadjuvant therapy?

**Operable**

- Improve surgical options
- Deliver adequate “adjuvant” chemotherapy
- Provide in vivo anti-tumour assessment
- Assess surrogate biologic endpoints for response & survival

**Goal**

**Inoperable**

**What are the indications for Neoadjuvant therapy?**

1970s
- Seminal First Step 1975
  - CMF p.o.

1980s
- Transition Era 1980 -1990
  - AC, FAC

1990s
- 3rd Generation Regimens 1990 -2000
  - Epirubicin Combinations: CEF/FEC
  - Questions of Dose
  - Sequential taxanes: AC→T
  - Combinations taxane: TAC
  - Which Taxane and Which Schedule

2000s
- Predictive Era 2000 +
  - Addition of Trastuzumab
  - Do ER+ tumors benefit from chemo
  - Are Anthracyclines Necessary?
  - Who benefits from Taxanes
  - Other biologics – antiangiogenics etc
Operable Breast Cancer: NSABP B-18

Operable Breast Cancer

Stratification
- Age
- Clinical Tumor Size
- Clinical Nodal Status

Operation
- AC x 4
  + TAM if >50 yrs.

AC x 4
  + TAM if >50 yrs

No difference in DFS and OS

Lumpectomy Rates
- 60% vs 68%
- Preop AC
  - cCR 36%
  - pCR 13%
Neoadjuvant therapy - Operable Breast Cancer

- Clinical response predicts overall survival
- Pathologic response predicts overall survival

Clinical results from B-18 shows:
- B-18 DFS by response
- B-18 OS by response

Wolmark N: CDC, 2000

Clinical response predicts overall survival
Pathologic response predicts overall survival

Operable Breast Cancer

DFS and OS by response:
- pCR
- pINV
- cPR
- cNR
Neoadjuvant Chemo – NON LABC

• **Benefits**
  - Assessment of response to chemo
  - Time for consideration of surgical options - ?BRCA+ etc
  - BCS in borderline situations
  - No delay in chemo

• **Risks**
  - Lack of knowledge of axilla unless SNLD is done prior
  - Delays surgery which in many cases may be the most important treatment
  - Clinical CR not usually a Pathological CR
  - Will the patient have the surgery?
Reminder of LABC

• LABC
  – 10 -15% of all new Breast Cancers
  – Higher incidence of HER2 +, young women, PABC
  – LABC, Inflammatory BC
  – Sometimes neglected, sometimes just aggressive

• **Prognosis is poor**
  – local recurrence
  – systemic relapse
  – overall survival
  – 15 yr OS
    • 20% IBC, 40% NIBC
Challenges/Objectives in the Neoadjuvantly treated Breast Cancer

- **Surgical oncology**
- Who to send for preoperative therapy?
- Role of breast conservation
- Role of SLN surgery
- Surgery on relapse

- **Medical oncology**
- What drugs to give for preoperative therapy?
- How can we improve response rates?
- What to give on relapse?

- **Radiation oncology**
- Combined chemo-rads?
- Role of breast conservation
- Radiotherapy for inoperable/progressive disease despite NAT
- Radiotherapy on relapse
Measuring Benefit from Neoadjuvant therapy

- Does response predict for overall survival?

- What is clinical CR?

- What is pathological CR?

- Does it affect surgical outcomes?
B-27 Schema (n=2,411)

Operable Breast Cancer

Randomization

AC x 4
Tam X 5 Yrs
Surgery

AC x 4
Tam X 5 Yrs
Docetaxel x 4
Surgery

AC x 4
Tam X 5 Yrs
Surgery

I
II
III
Clinical response and pathologic response are currently used as a surrogate of survival and as a tool to compare chemotherapy regimens.

NSABP B-27: Overall Survival - pCR vs. non-pCR patients (Bear JCO 2003)
Pathologic Response (pCR) in Breast

**B-27**

P < 0.001

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No Tumor</th>
<th>Non-Invasive</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td>13.7%</td>
<td>3.9%</td>
</tr>
<tr>
<td>(1,492 pts)</td>
<td></td>
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<tr>
<td>AC Docetaxel</td>
<td>25.6%</td>
<td>6.9%</td>
</tr>
<tr>
<td>(718 pts)</td>
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Non-Invasive Tumor Rates:
- AC: 9.8%
- AC Docetaxel: 18.7%

No Tumor Rates:
- AC: 6.9%
- AC Docetaxel: 25.6%
B-27: Nodal Down-staging

Aberdeen Trial  
\( n = 133 \) Patients \( T>3\text{cm} \) or IIIB

\[ \text{CVAP x 4} \rightarrow \text{Evaluation} \]

\[ \text{cCR/cPR (n=97)} \quad \text{R} \quad \text{cNC (n=45)} \]

\[ \text{CVAP x 4} \rightarrow \text{T x 4} \rightarrow \text{16\%} \]

\[ \text{T x 4} \rightarrow \text{34\%} \quad \text{pCR} \]

\[ \text{T x 4} \rightarrow \text{2\%} \]

\[ \text{CVAP: Cyclophosphamide, Vincristine, Doxorubicin, Prednisolone} \]

Progression-free Survival in the Aberdeen-Study (median F-up: 104 wks)

- Initial Response → Randomised to Docetaxel
- Initial Response → Randomised to CVAP
- No Initial Response → Non Randomised to Docetaxel

P = 0.022

Heys SD, Clin Breast Cancer 2002
Breast Cancer is not ONE Disease

Basal-like
HER-2
“Normal”
Luminal B
Luminal A

"Intrinsic" gene set on 78 single tumor samples

476 cDNA clones
85 Arrays

Sorlie T et al, PNAS 2001
Gene expression patterns of breast carcinomas distinguish tumour subclasses with clinical implications

Therese Sørlie a,b,c, Charles M. Perou a,d, Robert Tibshirani e, Turid Aas f, Stephanie Geisler g, Hilde Johnsen h, Trevor Hastie e, Michael B. Eisen h, Matt van de Rijn i, Stefanie S, Jeffrey l, Thor Thorsen k, Hanne Quist l, John C. Matese c, Patrick O. Brown m, David Botstein c, Per Eystein Lønning g, and Anne-Lise Børresen-Dale b,n
All Breast Cancer

ER+ 
65-75%

HER2+ 
15-20%

Basaloid 
~9%

BRCA like 
~6%
What is the “standard” for Her2-breast cancer in BC?

- **Neoadjuvant**
  - Any of our current adjuvant protocols
  - Dose dense AC-Paclitaxel
  - FEC – Doc
  - TAC
  - TC
  - AC
  - CMF
  - Hormones - AI

- **LABC**
  - AC- Docetaxel
  - FEC-DOC
  - TAC
  - Dose dense AC-Paclitaxel
  - Hormones - AI
Choosing Therapy by Responsiveness not just Risk

Targeted therapy
Understanding Response - Predictors
Individualizing Therapy
Understanding the Pharmacogenomics
Case Example

- 66 year old woman presents with a right breast mass, 3.5 cm in lower inner quadrant tethered to chest wall
- VERY anxious
- Treated with Letrozole 2.5 mg daily
- RT to breast and nodal area
- Mastectomy – after 4 months
- 1.4 cm residual disease resected
- Continued on letrozole with plans x 5 years
- All Breast Cancer
- ER+ 65-75%
- HER2+ 15-20%
- Basaloid ~9%
- BRCA like ~6%
Neoadjuvant Herceptin regimens exhibit high pCR rates (16 studies, 1,226 patients)

- Antón et al 2007, n=26 My + P + H
- Untch et al 2008, n=452 EC + H
- Coudert et al 2007, n=70 EC → P + H
- Limentani et al 2007, n=31 D + H
- Tripathy et al 2007, n=28 P + X + H
- Marty et al 2007, n=30 My + P + H
- Harris et al 2003, n=40 V + H (including IBC)
- Hurley et al 2002, n=48 D + cisplatin + H (including IBC)
- Kelly et al 2006, n=37 AC → P + H (including IBC)
- Burstein et al 2003, n=40 P + H (including IBC)
- Bines et al 2003, n=32 D + H

\(^{a}\)X was given either concurrently or sequentially with D + H
EC, epirubicin, cyclophosphamide; FEC, 5-fluorouracil, epirubicin, cyclophosphamide
My, Myocet; X, Xeloda
Neoadjuvant Trastuzumab

• Buzdar et al

Her2+ operable breast cancer

P X 4 + FEC x 4

P X 4 + FEC x 4 + concurrent Trastuzumab x 24 wks

pCR Results

26%

62.5%

Planned sample size 164

Study closed after 42 pts accrued due to better than expected results
NOAH: the largest neoadjuvant trial in HER2-positive breast cancer

HER2-positive LABC (IHC 3+ and / or FISH+)

- n=115
- H + AT q3w x 3
- H + T q3w x 4
- H q3w x 4 + CMF q4w x 3
- Surgery followed by radiotherapy
- H continued q3w to Week 52

HER2-negative LABC (IHC 0/1+)

- n=113
- AT q3w x 3
- T q3w x 4
- CMF q4w x 3
- Surgery followed by radiotherapy

- n=99
- AT q3w x 3
- T q3w x 4
- CMF q4w x 3
- Surgery followed by radiotherapy

aHormone receptor-positive patients receive adjuvant tamoxifen; LABC, locally advanced breast cancer; H, trastuzumab (8 mg/kg loading then 6 mg/kg); AT, doxorubicin (60 mg/m²), paclitaxel (150 mg/m²); T, paclitaxel (175 mg/m²); CMF, cyclophosphamide, methotrexate, fluorouracil
Neoadjuvant Herceptin significantly improves pCR rates in the NOAH trial

pCR, pathological complete response in the breast
IBC, inflammatory breast cancer

Baselga et al 2007; Gianni et al 2007
GeparQuattro

N=1500

Stratified acc. to Early Response

Epirubicin 90 mg/m²
Cyclophosphamide 600 mg/m²
Docetaxel 100 mg/m² (A)
75 mg/m² (B,C)
Capecitabine 1800 mg/m²
If Her2 pos: Trastuzumab 6 mg/kg q3w 1y
If endocrine responsive Tam/AIs
Pathologic Complete Response (pCR)

Untch M et al. EBCC 2008
pCR According to Tumour Stage*

*Predefined and stratified
pCR, pathological complete response

Untch M et al. EBCC 2008
What is the “standard” Her2+ in BC?

• Staging with MUGA or Echo
• Initiation of chemotherapy with
  – AC – dose dense or three weekly followed by Docetaxel /or paclitaxel and Herceptin x 4
  – FEC – followed by Docetaxel and Herceptin x 3
  – TCH – docetaxel/carbo/herceptin x 6
  – Herceptin continuing for a year
• Radiation and Surgery
• Hormonal therapy if ER/PR positive
Trials that are pending
NSABP B-40
Her2 Neg ≥2cm

Endpoints: pCR; 2⁰ endpoint: pCR Δ (29→38%)
DFS N=1200 Started: 11-07
NSABP B-41
Her2 Pos

Operable BC

R

AC X 4
Paclitaxel/wk + Trastuzumab

AC X 4
Paclitaxel/wk + Lapatinib

AC X 4
Paclitaxel/wk + Lapatinib + Trastuzumab

Surgery

Tmb

N=522; pCR Δ 22% (42→64%)
Invasive breast cancer
HER2+
T>2 cm
(inflammatory BC excluded)
LVEF ≥ 50%

N=450

Stratification:
— T<5 cm versus T>5 cm
— ER or PgR + versus both
ER and PgR –
— N0-1 versus N ≥2
— Conservative surgery or not

Randomize

Surgery

FEC × 3

18 weeks 9 weeks 34 weeks

52 weeks of anti-ErbB2 therapy
GeparQuinto study: neoadjuvant Herceptin vs lapatinib

HER2-positive primary breast cancer (IHC 3+ or central FISH+)
n=594

- Epirubicin + cyclophosphamide + Herceptin q3w x 4
- Docetaxel q3w x 4 + Herceptin q3w x 4
- Epirubicin + cyclophosphamide q3w x 4 + lapatinib 1,250 mg qd
- Docetaxel q3w x 4 + lapatinib 1,250 mg qd

Surgery

Herceptin q3w until Week 52

Docetaxel 75 mg/m² q3w x 4; epirubicin 90 mg/m² + cyclophosphamide 600 mg/m² q3w x 4; Herceptin 8 mg/kg loading dose followed by 6 mg/kg q3w for 12 months; lapatinib 1,250 mg/day for 24 weeks
Neosphere study: neoadjuvant Herceptin + pertuzumab

HER2-positive LABC and large stage II breast cancer (n=400)

- Herceptin + docetaxel q3w x 4
  - Surgery
  - FEC q3w x 3
  - Herceptin q3w until Week 52

- Herceptin + docetaxel + pertuzumab q3w x 4
  - Surgery
  - FEC q3w x 3
  - Herceptin q3w until Week 52

- Herceptin + pertuzumab q3w x 4
  - Surgery
  - Herceptin + docetaxel q3w x 4
  - FEC q3w x 3
  - Herceptin q3w until Week 52

- Pertuzumab + docetaxel q3w x 4
  - Surgery
  - FEC q3w x 3
  - Herceptin q3w until Week 52
But is chemotherapy the answer to all the questions in LABC?
Our most successful therapies target self-sufficiency in growth signals

**Growth Factor**
- Estrogen/ER
- HER2

**Therapy**
- SERMs, AIs, oophorectomy, fulvestrant
- Trastuzumab
  - Lapatinib
How effective is Neoadjuvant Chemotherapy in ER+ Breast Cancer

- Chemotherapy is less effective in ER+ disease vs ER- disease (but doesn’t mean some patients don’t benefit)

- Doe Luminal A benefit vs luminal B or others?

- Other predictive markers needed for taxane sensitivity? Other new agents?
Phase III SWOG 8814 (TBCI 0100)
Postmenopausal, N+, ER+

RANDOMIZE

n = 1477

- tamoxifen x 5 yrs (n = 361)
- CAF x 6, with concurrent tam (n = 550)
- CAF x 6, then tamoxifen (n = 566)

Superior Disease-Free Survival (DFS) and Overall Survival (OS) over 10 Years

No benefit to CAF over time if low RS (n=146)

Strong benefit if high RS

Disease-Free Survival by Treatment

Low risk (RS < 18)

Stratified log-rank p = 0.97 at 10 years

Disease-Free Survival by Treatment

High risk (RS ≥31)

Stratified log-rank p = 0.033 at 10 years

Disease-Free Survival by Treatment

Intermediate risk (RS 18-30)

Stratified log-rank p = 0.48 at 10 years
No DFS Benefit from CAF if Central IHC is Both HER2 Negative and ER Level High* (n=142)

*Test for Interaction p=0.052
Surely neoadjuvant chemotherapy is the best?

- Semiglazov et al. PASCO 2004
  - neoadjuvant treatment in women aged >70 with ER + breast cancer
    - Doxorubicin and Paclitaxel (q3 weeks, 4 cycles) (n=60)
    - 3 months treatment with anastrozole or exemestane (n=59)

- There was a trend towards more breast conservation in the AI arms.

<table>
<thead>
<tr>
<th></th>
<th>chemotherapy</th>
<th>anastrozole</th>
<th>exemestane</th>
</tr>
</thead>
<tbody>
<tr>
<td>pathological CRs</td>
<td>7.4%</td>
<td>3.3%</td>
<td>6.8%</td>
</tr>
<tr>
<td>overall clinical RRs</td>
<td>76%</td>
<td>75%</td>
<td>81%</td>
</tr>
</tbody>
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Challenges in the Management of LABC

What are the response rates like in the real world?

Clinical
Pathological
Challenges in the Management of LABC

Should patients with LABC have a lumpectomy if good response to chemotherapy?
Pre-Treatment MRI of Breast Cancer with Septal Spread

After Neo-Adjuvant Chemotherapy
Tumour shrunk to lesser volume along septa
<table>
<thead>
<tr>
<th>Study</th>
<th>Definition</th>
<th>pCR rate (n=117) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP</td>
<td>pCR in breast only</td>
<td>10.3</td>
</tr>
<tr>
<td></td>
<td>No microinvasive disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Can have DCIS</td>
<td></td>
</tr>
<tr>
<td>Aberdeen</td>
<td>pCR in breast/axilla</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>No microinvasive disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Can have DCIS</td>
<td></td>
</tr>
<tr>
<td><strong>TSRCC</strong></td>
<td>pCR in breast and axilla</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>No microinvasive disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Can have DCIS</td>
<td></td>
</tr>
<tr>
<td>Chevallier</td>
<td>pCR in breast and axilla</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>No microinvasive disease</td>
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</tr>
<tr>
<td></td>
<td>No DCIS</td>
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</tbody>
</table>
Challenges in the Management of LABC

Should we treat patients with residual lymph node involvement after neoadjuvant chemotherapy with further adjuvant chemotherapy?
Should we treat patients with residual lymph node involvement after neoadjuvant chemotherapy with further adjuvant chemotherapy?

NSABP B-27: Overall Survival nodal Status; Patients without pCR

(Bear JCO 2003)
Gepartrio Pilot

T \geq 2 \text{ cm} \quad \text{Palpation} \quad \text{NC} \quad \text{Randomize} \quad \text{PR or CR} \quad \text{Her}-2

\begin{align*}
\text{TAC} & \quad \text{Docetaxel} \quad 75 \text{ mg/m}^2 \\
& \quad \text{Doxorubicin} \quad 50 \text{ mg/m}^2 \\
& \quad \text{Cyclophosphamide} \quad 500 \text{ mg/m}^2 \\
\text{NX} & \quad \text{Vinorelbine} \quad 25 \text{ mg/m}^2, \text{ Days 1 and 8} \\
& \quad \text{Capecitabine} \quad 2000 \text{ mg/m}^2, \text{ Days 1–14}
\end{align*}

\text{pCR} \quad 51\% \quad \text{cCR} \quad 22\%

\text{NX} \quad 3\%

\text{TAC} \quad 7\%

\text{TAC x 6} \quad 28\%
Systemic therapy – when more is less!

- LABC or neoadjuvant patients not responding to chemotherapy
  - More or different chemo is not always the answer
  - Chemo is toxic
  - Importance of multidisciplinary team
  - Unique area for further study:
    - Role of RT
    - Role of biologics
    - Understanding chemo-resistance
    - Response predictors
    - Response Assessment Tools
Challenges

Surgical oncology

• Who to send for preoperative therapy?
  – In the setting of LABC – we are hoping to make surgery feasible
  – This is different from using NAT as the standard for ALL patients

• Role of breast conservation
  – Not common for LABC population
  – Can be done when feasible

• Role of SLN surgery
  – Very high rate of nodal involvement

• Surgery on relapse
  – Palliation in the setting of very poor prognosis
Summary

Preoperative vs. Postoperative
  – OS = DFS = ↑BCS

Clinical and pathologic response predicts overall survival

Standard chemo is an anthracycline & taxane regimen for HER2 negative with the addition of herceptin for HER2 positive

For older HR+ pts consider endocrine therapy

Currently no role for more chemo for patients with residual disease after preoperative therapy
“Og discovered fire, and Thorak invented the wheel. There’s nothing left for us.”