HER2 overexpressie en het mammacarcinoom; klinische implicaties

Hans Nortier
Afdeling Klinische Oncologie LUMC
29-1-2010

HER2-positive status verkort de overleving???

- Vrouwen waarvan de borstkanker ook HER2-positief zijn hebben kortere totale overleving
- 20% – 30% hebben een overexpressie

Mediale overleving
HER2 positive 3 jaar
HER2 negative 6–7 jaar

Slamon DJ et al. Science 1987;235:177–82

HER receptoren

HER1 HER2 HER3 HER4

HER receptor ligand-binding

Ligand

Slamon DJ et al. Science 1987;235:177–82
Conformational change

Dimerization domain

Receptor dimerization

The receptor tyrosine kinase domain

Phosphorylation of the receptor tyrosine kinase domain
Recruitment of adaptor proteins

Initiation of signaling pathways

Cytoplasmic signaling cascades

Relaying the message to the nucleus
Activation of target genes

4

Normale EGFR/erbB-2 expressie

Cell surface
EGFR protein (receptor)
Other EGFR/HER family receptor
Cell nucleus

Sliwkowski MX. Semin Oncol. 1999;26(suppl 12):60-70.

EGFR/erbB-2 Overexpressie bij het Mammarcinoom

>10- to 100-x het niveau van normale expressie
Excess receptors lead to sustained signaling

Activated receptors

Growth signal
Cell nucleus

HER2 receptor dimer transmembrane signal transduction pathway

Growth factor
Binding site
Plasma membrane
Signal transduction to nucleus
Cytoplasm
Nucleus
Gene activation
CELL DIVISION
Lapatinib (Tyverb®)

Lapatinib is the first-in-class oral small-molecule inhibitor of EGFR/HER2 tyrosine kinase:

- Belongs to the 4-anilinoquinazoline class of tyrosine kinase inhibitors
- Binds reversibly to the cytoplasmic ATP-binding site of the kinase, thereby preventing receptor phosphorylation and activation
- Works intracellularly

Lapatinib: Mechanism of Action

- Receptor accumulation!
- Receptor is downregulated
- Activation of ADCC
- More potent inhibitor of signaling!

NEW INSIGHTS INTO THE MECHANISM OF ACTION OF L vs T

Trastuzumab (T)
- Receptor is downregulated
- Activation of ADCC
- More potent inhibitor of signaling!

Lapatinib (L)
- Receptor accumulates
- Inhibition of:
  - HER2 phosphorylation
  - HER2 dimerization
  - HER2-NEK2
  - HER2-ERK1
  - HER2-ERK3

Combination
- Potential enhancement of ADCC through HER2 stabilization at the membrane level

anti-ErbB2 strategy

mAbs
- Bind to extracellular receptor
- May be inactive for truncated receptors
- IV
- Expensive

Small molecule TKIs
- Inhibit intracellular kinase domain
- Active for truncated receptor
- Oral
- More « affordable »

Courtesy of J. Baselga
MECHANISMS OF RESISTANCE TO TRASTUZUMAB

- p95—HER2 truncated form
- HER1—HER3 signalling
- Lateral signalling

Courtesy of J. Baselga

CASUS Lapatinib expanded Acces Program (LEAP)

- Klinisch beeld:
  - 38-jarige vrouw
  - Erytheem en induratie tpi mastectomie litteken rechts
  - Geen koorts
- Voorgeschiedenis:
  - Status na adenocarcinoom rechter mamma → mastectomie en lymfkiertoilet (2005)
  - Botmetastasen (2005)
- Medicatie:
  - trastuzumab/docetaxel/vinorelbine/ APD-infusen

Histologisch onderzoek

Her2-neu kleuring
**Differentiaal diagnose**

Carcinoma erysipeloides  
Erysipelas

PA: atypische cellen  
PA: reactieve veranderingen

**Behandeling**

• Omgezet naar:
  - Lapatinib (Tykerb®)
  - Capecitabine (Xeloda®)

  → Complete remissie

**LEAP  San Antonio 2007**

• 2,497 pts at 355 centers worldwide
• The most frequently:
  • SAEs: diarrhea (10%), N/V (4%) and dehydration (3%)
  • AEs: diarrhea, N and hand-foot syndrome
• Incidence of serious cardiac dysfunction: 0.5%
• Incidence of serious pneumonitis: 0.2%
• This study confirmed that in pretreated HER2+ pts, lapatinib + capecitabine is well tolerated

**Adjuvant Herceptin trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. patients</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA</td>
<td>5090</td>
<td>Piccart-Gebhart et al 2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Smith et al 2007</td>
</tr>
<tr>
<td>NSABP B-31</td>
<td>2030</td>
<td>Romond et al 2005</td>
</tr>
<tr>
<td>NCCTG N9831</td>
<td>3505</td>
<td>Romond et al 2005</td>
</tr>
<tr>
<td>BCIRG 006</td>
<td>2222</td>
<td>Slamon et al 2006</td>
</tr>
<tr>
<td>FinHer</td>
<td>232(^a)</td>
<td>Joensuu et al 2006</td>
</tr>
</tbody>
</table>

\(^a\)HER2-positive subgroup
**Pivotal adjuvant Herceptin trials: patient characteristics**

- HER2 positive (IHC 3+ / FISH+)
- Invasive breast cancer resected by lumpectomy / mastectomy
- Nodal status
  - node positive (NSABP B-31)
  - node positive or high-risk node negative (NCCTG N9831, HERA, BCIRG 006)
- Known hormone receptor status
  (ER / PgR or ER alone)
- No previous or current cardiac disease

ER, oestrogen receptor; IHC, immunohistochemistry; FISH, fluorescence in situ hybridisation; PgR, progesterone receptor

**HERA trial design**

- IHC or FISH (n=5090)
- Observation
- Standard chemotherapy
- 1 year Herceptin
- 2 years Herceptin

**HERA trial: recent developments**

- Median follow-up increased to 2 years
- 539 DFS events observed in both arms
- 861 observation patients switched to Herceptin
- ITT and censored population subgroup analysis
- 149 deaths have occurred
- n=90 observation vs n=59 Herceptin
- Difference in distant metastases reported
- n=233 observation vs n=152 Herceptin

DFS, disease-free survival; ITT, intent-to-treat population

**HERA trial: DFS (ITT population; median 2 year follow-up)**

- 95% CI 0.54, 0.76
- HR 0.64
- 3 year DFS 80.6%

Smith et al 2007
**HERA trial: OS (ITT population; median 2 year follow-up)**

- **OS, overall survival**
- **33 months from randomisation**
- **1 year Herceptin**
- **Deaths**
- **3 year OS**
- **HR**
- **95% CI**
- **p value**
- **No. at risk**
- **Patients (%)**
- **HR = 0.66; p = 0.0115**

**HERA trial: exploratory DFS subgroup analysis (ITT) 1 year Herceptin vs observation**

- **Subgroup (no. patients)**
  - Age at randomisation
    - <35 years (253)
    - 35-49 years (1508)
    - 50-59 years (1096)
    - ≥60 years (544)
  - Nodal status
    - Not assessed (neoadjuvant chemotherapy) (372)
    - Negative (1099)
    - 1-3 positive nodes (976)
    - ≥4 positive nodes (953)
  - Tumour size
    - Any (neoadjuvant chemotherapy) (372)
    - 0-2 cm (1351)
    - >2-5 cm (1482)
    - >5 cm (171)
  - Hormone receptor status
    - ER+ / PR- (460)
    - ER+ / PR+ (984)
    - ER- / PR- (1627)
  - All patients (3401)

**NSABP B-31 and NCCTG N9831: combined analysis**

- **IHC or FISH (n=2030)**
  - NSABP B-31
  - NCCTG N9831

**B-31 and N9831 combined analysis: DFS**

- **Patients (%)**
- **2 year median follow-up**
- **n**
- **Events**
- **HR = 0.48; p < 0.0001**
- **AC, doxorubicin + cyclophosphamide; H, Herceptin; P, paclitaxel**

**Notes:**
- Smith et al. 2007
- Romond et al. 2005
**B-31 and N9831 combined analysis: OS**

- 2 year median follow-up
- Patients (%): 94%, 91%, 87%, 92%
- HR = 0.67; p = 0.015

**BCIRG 006 trial design**

- FISH (n=3222)
- Herceptin 1 year
- AC/DH vs AC/D
- HR = 0.61; p < 0.0001
- DCarboH vs AC/D
- HR = 0.67; p = 0.0003

**BCIRG 006: recent developments**

- Median follow-up increased to 3 years
- 462 DFS events observed in 3 arms
- 17 control patients switched to Herceptin
  - ITT population subgroup analysis
- 185 deaths have occurred
  - 160 breast cancer deaths
  - 44 in AC/DH; 47 in DCarboH; 69 in AC/D

**BCIRG 006: DFS 2nd interim analysis**

- Patients (%): 93%, 92%, 87%
- HR (AC/DH vs AC/D) = 0.61; p < 0.0001
- HR (DCarboH vs AC/D) = 0.67; p = 0.0003
**BCIRG 006: OS 2nd interim analysis**

- Patients (%): 100, 90, 80, 70, 60, 50
- Deaths: AC (n=1073), AC + DH (n=1074), AC + DCarboH (n=1075)
- HR (AC + DH vs AC): 0.59, p=0.004
- HR (DCarboH vs AC + D): 0.86, p=0.017

- Slamon et al 2006

**FinHer trial design / randomisations**

- 1010 pts
- EBC pN+ or pN0 (tumour >2 cm, PgR-)
- AC / V vinorelbine
- DH
- F, fluorouracil; E, epirubicin; C, cyclophosphamide

- 1010 patients were recruited and, after 2 randomisations, allocated to 6 treatment arms (1 patient excluded from efficacy analyses)

- PgR, progesterone receptor; R, fluorouracil; E, epirubicin; C, cyclophosphamide

**Adjuvant Herceptin trials: summary of DFS data to date**

- HERA (n=5090)
- Combined analysis (n=3351)
- BCIRG 006 AC + DH (n=1074)
- BCIRG 006 DCarboH (n=1075)

- FinHer VH / DH* (n=232)

- Median follow-up:
  - 2 years
  - 3 years

- Favours Herceptin
- Favours no Herceptin

- HR

- *Relapse-free survival; V, vinorelbine

- Romond et al 2005; Joensuu et al 2006; Slamon et al 2006; Smith et al 2007

**Adjuvant Herceptin trials: summary of OS data to date**

- HERA Herceptin 1 year arm
- Combined analysis
- BCIRG 006 AC + DH
- BCIRG 006 DCarboH

- FinHer VH / DH

- Median follow-up:
  - 2 years
  - 3 years

- Favours Herceptin
- Favours no Herceptin

- HR

- p=NS

- NS, not significant

- Joensuu et al 2006; Romond et al 2005; Slamon et al 2006; Smith et al 2007
Adjuvant Herceptin: answering some key questions

- Optimal duration of Herceptin treatment?
  - HERA (1 year versus 2 years Herceptin)
- Effect of delayed switching to Herceptin?
  - HERA
- Is concurrent or sequential Herceptin administration optimal?
  - NCCTG N9831
- Does rechallenging with Herceptin provide further benefit for patients?
  - Retreatment after HErceptin Adjuvant (RHEA) trial

Conclusions

- Results from four major randomised trials provide level 1 evidence for OS benefit of adjuvant Herceptin
- Adjuvant Herceptin greatly increases the chance of survival for patients with HER2-positive EBC
- Adjuvant Herceptin should be considered for all patients with HER2-positive breast cancer

Adjuvant Trastuzumab Weighing Benefits Versus Risks

**BENEFITS**

- Risk of recurrence reduced by half
  - Shown in 5 clinical trials and >13,000 women!

**RISKS**

- Severe cardiac insufficiency: 0.5% to 3.4%
  - Shown in 5 clinical trials and >13,000 women!

Can we improve upon these results?
Locally-determined HER2-positive invasive breast cancer (For patients with neoadjuvant treatment, the Her2 determination should be done on a tissue sample taken before the treatment is started)

Centrally-determined HER2 +

Surgery, complete (neo)adjuvant anthracycline-based chemotherapy

LVEF ≥ 50

Lapatinib + 3-weekly trastuzumab 40 weeks

Lapatinib + Weekly trastuzumab 12 weeks

Weekly trastuzumab 12 weeks

Lapatinib 52 weeks

Weekly paclitaxel 12 weeks

Weekly paclitaxel 12 weeks

Radiotherapy (if indicated)

Randomization

Conclusions

Metastatic Breast Cancer

"targeted therapy":

HER2 – overexpression:

Trastuzumab

Lapatinib

cleaner agents

Luminal B (low content of hormonal receptors)

IgF-1 blockers?

Triple negative:

PARP inhibitors

VEGF-inhibitors

Other TKI’s?
Conclusions

- Results from four major randomised trials provide level 1 evidence for OS benefit of adjuvant Herceptin.

- Adjuvant Herceptin greatly increases the chance of SURVIVAL for patients with HER2-positive EBC.

- Adjuvant Herceptin should be considered for all patients with HER2-positive breast cancer.

54, postmeno, N0, 2.8 cm, gr III, ER+, HER2 +++
voorspelde 10 jaars overleving

- 1995: geen adjuvante systeemtherapie = 73%
- 1998: tamoxifen 2 jaar = 77%
- 2000: tamoxifen 5 jaar = 80%
- 2002: tamoxifen 5 jaar +/- AC of CMF = 82%
- 2005: AC-T + trastuzumab + aromataseremmer = 91%
- 2008: ALTTO studie > 91%