Can new prognostic tools help us to design adjuvant treatment in elderly?

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Medical Oncology

HÔPITAL RENÉ HUGUENIN

Au 1er janvier 2010, le Centre René Huguenin devient l'Hôpital René Huguenin, un établissement de soins, d’enseignement et de recherche de l’Institut Curie
## Disclosures

<table>
<thead>
<tr>
<th>Role</th>
<th>Companies</th>
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<tbody>
<tr>
<td>Research Support/P.I.</td>
<td>Cephalon, Amgen, Ipsogen</td>
</tr>
<tr>
<td>Employee</td>
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<tr>
<td>Consultant</td>
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<tr>
<td>Major Stockholder</td>
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<td>Speakers Bureau</td>
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<td>Honoraria</td>
<td>Cephalon, Roche, Janssen, GSK, Amgen</td>
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<td>Scientific Advisory Board</td>
<td>Cephalon, Roche, Janssen, Amgen</td>
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Adjuvant chemo for breast cancer

**DFS**

- **All**
  - CALGB (1975-1999)
  - 4 randomized trials
  - 6487 pts

- **≤50**
  - > 65 yo 542 (8%)
  - > 70 yo 159 (2%)

- **51-64**

- **≥65**

**OS**

- **All**
- **≤50**
- **51-64**
- **≥65**

**Results**

- Benefit: identical
- Toxicity: careful!!
- Toxic deaths 1.5%

Muss, JAMA 2005
CALGB / CTSU 49907

DFS

OS

All

ER+

ER−

Muss, NEJM 2009
• British Columbia Cancer Agency
• 1986-1992
• 4,046 pts

• Jules Bordet
• 2,723 pts

Cheung, CROH 2008; Durbecq, CROH 2008
## IHC vs microarray & limitations!!!

<table>
<thead>
<tr>
<th></th>
<th>Basal like (%)</th>
<th>Luminal A (%)</th>
<th>Luminal B (%)</th>
<th>HER2-like (%)</th>
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</thead>
<tbody>
<tr>
<td>HER2+ (IHC)</td>
<td>10</td>
<td>12</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>ER+ (IHC)</td>
<td>12</td>
<td>96</td>
<td>97</td>
<td>46</td>
</tr>
<tr>
<td>Grade III</td>
<td>84</td>
<td>19</td>
<td>53</td>
<td>74</td>
</tr>
<tr>
<td>pT &gt; 2 cm</td>
<td>75</td>
<td>53</td>
<td>69</td>
<td>74</td>
</tr>
<tr>
<td>pN+</td>
<td>40</td>
<td>52</td>
<td>65</td>
<td>66</td>
</tr>
</tbody>
</table>

- > 200 molecular markers
  - HER2, EGFR/HER1, CCND1, p53, BCL2/BAX, uPA/PAI-I, VEGF, etc
- None recommended in daily practice except monogenic!!! ER, HER2, Ki67
- Signatures (multigene assays = several diagnostic questions simultaneously)?
  - Handicaps!!
    - Validation, gene sets do not confirm each other
    - Overdependence on proliferation-related genes
    - Associated costs, necessary and complex bioinformatics
  - Examples
    - Oncotype DX® (21 genes),
    - Mammaprint® (70 genes)
    - MapQuant Dx® (GGI, 97 genes)
    - Theros® Breast Cancer Index SM (HOXB13/IL17R + 5 genes of the molecular-grade index), BLN Assay, ARUP Breast Bioclassifier, Celera Metastatic Score, eXagen BCtm, Invasive Gene Signature, Wound Response Indicator, Mammostrat, PAM50

A GENE-EXPRESSION SIGNATURE AS A PREDICTOR OF SURVIVAL IN BREAST CANCER

B St. Gallen Criteria

A Gene-Expression Profiling

295 pts < 53 yo

25,000 genes, 78 tumours, 70 genes, 17 pN0, all < 55 yo

van’t Veer, Nature 2002; van de Vijver, NEJM 2002
MINDACT

- 6,600 pts < 70
  - FEB 2007-AUG 2011
  - 11,291 registered pts
  - 6,673 enrolled (59.1%)
Oncotype DX®

- qRT-PCR assay for FFPE
  - 21 genes
    - 16 cancer related and 5 reference genes
    - Population ER+

- Prognosis
  - pN0 (NSABP B14 & NSABP B20: both < 70)
  - pN+ (SWOG 8814: 13% 70+)
  - ATAC

<table>
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<tr>
<th>RS</th>
<th>10-yr met relapse</th>
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<tr>
<td>≥ 31</td>
<td>30.5 (23.6-37.4)</td>
</tr>
<tr>
<td>18-31</td>
<td>14.3 (8.3-20.3)</td>
</tr>
<tr>
<td>&lt; 18</td>
<td>6.8 (4-9.6)</td>
</tr>
</tbody>
</table>

- Indication for chemotherapy?
  - NSABP B20
  - SWOG 8814 (only during 5 first years)
  - TAILORx (2006)

Dowett, J Clin Oncol 2010
Distant RFS NSABP B20

Paik S et al. JCO 2006;24:3726-3734
TAILORRx

- Group 1: RS < 11
  - HT

- Group 2: RS 11-25
  - CT + HT
  - HT

- Group 3: RS > 25
  - CT + HT

- pN0 ≤75

- 11,248 pts
- March 2006
- 1/ DFS 2/ DRFI, RFI, OS, FACT

http://www.clinicaltrials.gov/ct2/home
SWOG 1007 RxPONDER

- 9,400 pts 18+ screened
- 4,000 pts randomized
- 1/ DFS
- 2/ safety, RS vs PAM50, QoL

http://www.swog.org/
High False-Negative Rate of HER2 Quantitative Reverse Transcription Polymerase Chain Reaction of the Oncotype DX Test: An Independent Quality Assurance Study

David J. Dobbs, Molly E. Klein, Syed E. Mehmood, Raymond T. Tabe, Yongli Shuai, and Rohit Bhargava

ABSTRACT

Purpose
HER2 (ERBB2) status is an important prognostic and predictive marker in breast carcinoma. In recent years, Genomic Health (GH), purveyor of the Oncotype DX test, has been separately reporting HER2 by reverse transcription polymerase chain reaction (RT-PCR) to oncologists. Because of the lack of independent evaluation, this quality assurance study was undertaken to define the concordance rate between immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) and GH RT-PCR HER2 assay.

Methods
All patients at three participating laboratories (Magee-Womens Hospital [Pittsburgh, PA], Cleveland Clinic [Cleveland, OH], and Riverside Methodist Hospital [Columbus, OH]) with available HER2 RT-PCR results from GH were included in this study. All IHC-positive and equivocal patient cases were further evaluated and classified by FISH at respective laboratories.

Results
Of the total 843 patient cases, 784 (93%) were classified as negative, 36 (4%) as positive, and 23 (3%) as equivocal at the three institutions using IHC/FISH. Of the 784 negative patient cases, 778 (99%) were also classified as negative by GH RT-PCR assay. However, all 23 equivocal patient cases were reported as negative by GH. Of the 36 positive cases, only 10 (29%) of GH C1, 14% to 45% were reported as positive, 12 (33%) as equivocal, and 14 (39%) as negative.

Conclusion
There was an unacceptable false-negative rate for HER2 status with GH HER2 assay in this independent study. This could create confusion in the decision-making process for targeted treatment and potentially lead to mismanagement of patients with breast cancer if only GH HER2 information is used.

Quantitative Reverse Transcriptase Polymerase Chain Reaction and the Oncotype DX Test for Assessment of Human Epidermal Growth Factor Receptor 2 Status: Time to Reflect Again?

John M.S. Bartlett, Ontario Institute for Cancer Research, Toronto, Ontario; Edinburgh Cancer Research Centre, University of Edinburgh, Edinburgh, United Kingdom
Jane Starczynski, Ontario Institute for Cancer Research, Toronto, Ontario
Hazard of recurrence

Fig 4. Annual hazard of recurrence of 3,562 patients separated by ER status. The mean follow-up times for ER-positive and ER-negative patients were 8.1 and 8.0 years, respectively. (ER status was missing for 23 patients.)

Saphner, J Clin Oncol 1996; Park, Cancer Chemother Pharmacol 2010
Cumulative probability of death from ER- BC vs other causes (SEER 1990–2000)

Age at diagnosis

<50  50-59  60-69  70+

pT1

pT2

pN1

Schairer, JNCI 2004
Cumulative probability of death from **ER+ BC** vs other causes (SEER 1990–2000)

**Age at diagnosis**

- <50
- 50-59
- 60-69
- 70+

**Time since diagnosis (months)**

- **pT1**
- **pT2**
- **pN1**

Schairer, JNCI 2004
Life expectancy

pT, pN, type, grade ER, HER2

TNM NPI Adjuvant! Online

Microarray qRT-PCR

Heterogeneity of ageing

CGA
AAAdjuvant systemic treatment for oestrogen-receptor (ER)-positive HER2-negative breast carcinoma in women over 70 according to Genomic Grade (GG): chemotherapy + endocrine treatment versus endocrine treatment. A French UNICANCER Geriatric Oncology Group (GERICO) and Breast Group (UCBG) multicentre phase III trial
Improvement of the clinical applicability of the Genomic Grade Index through a qRT-PCR test performed on frozen and formalin-fixed paraffin-embedded tissues

Jérôme Toussaint¹, Anrieta M Sieuwerts¹², Benjamin Haibe-Kains³, Christine Desmedt¹, Ghizlane Rouas¹, Adrian I Harris¹, Denis Larsimont¹, Martine Piccart¹, John A Foekens², Virginie Durbecq¹ and Christos Sotiriou*¹

8 genes (4 reporter + 4 reference)
9 genes (6 reporter + 3 reference)

Toussaint, BMC Genomics 2009
ASTER 70s - Design

EBC ≥70 yo
Surgery

ER+ HER2-
Lee’s score§
G8 score

Group I
high GG
by RT-PCR

Group II
low GG
by RT-PCR

Arm A = HT**

Arm B = CT + HT**

HT
hormonotherapy 5 years

CT
4 cycles (TC, AC or MC) + GCSF

**
± XRT according to standard guidelines

NO CHEMOTHERAPY IS RECOMMENDED
Follow up + inclusions in other studies (e.g. ELD15 validation)
- Low GG
- Other causes for non inclusion (refusal, geriatrics, etc.)
Patients will be offered HT according to standard guidelines

700 pts (+ 1100-1300 not included i.e. low GG or other causes followed up)
1/ 4-yr OS
2/ Tolerance, DFS, QoL (ELD15), Q-TWIST, G8,
cost-effectiveness analysis, GG/RT-PCR, TR, geriatrics

Phase III w/ 4-yr OS
Hypothesis B > A
Δ 7.5% (A 80% vs B 87.5%) HR 0.60
Inclusion period 4 years
170/year
Follow up 4 years
129 events
α 5% β 20%
340 pts/arm
Conclusions

• **ER- patients: a “too simple” question**
  – Predictive tools are lacking

• **ER+ patients: urgent to better evaluate competing risks**
  – GEP: better definition of cancer prognosis in order not to deprive those who might derive a real benefit from additional treatment
    • To develop specific tools
    • To implement and/or validate those developed for younger patients
  – CGA: better (more frequent!) assessment of comorbidities & functional status

Increase research on these aspects from a prejudice-based to an evidence-based medicine...