Predicting Treatment Responses in Breast Cancer Using Genomic Tools

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Leader, Breast Oncology Program
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Disclosure of Relevant Financial Relationships

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Relevant Disclosures

- Speaker’s Bureau: Genomic Health
- Consultant: Biotheranostics

Overview

- Predicting response to therapy in early stage breast cancer
- Predictors of targeted therapy
- Tumor evolution
- Actionable mutations

The Lancet July 11, 1896

ON THE TREATMENT OF INOPERABLE CASES OF CARCINOMA OF THE MAMMA: SUGGESTIONS FOR A NEW METHOD OF TREATMENT, WITH ILLUSTRATIVE CASES.1

BY GEORGE THOMAS BEATSON, M.D. EDIN.
SURGEON TO THE GLASGOW CANCER HOSPITAL; ASSISTANT SURGEON, GLASGOW WESTERN INFIRMARY; AND EXAMINER IN SURGERY TO THE UNIVERSITY OF EDINBURGH

__________________

“Apsley-place, May 6th, 1895

Dear Dr. Beatson,—The bearer is, and has been, suffering, I fear, from a malignant breast. She has been in the Royal Infirmary before she came to me. My own opinion is that nothing can be done for her, but as she is a woman of great courage you might have a look at it for my sake, and perhaps you can order her something in the way of dressing. Even this little will be accepted by her as a great deal.

With kindest regards, yours very truly,

James W. Wallace."

Love

RR,

Philips

J.


Hormonal Therapy for Advanced Breast Cancer: Milestones


- Oophorectomy and its response to advanced disease (George Beatson)
- Immuno-histochemistry developed for ER and PR analysis
- ER downregulator approved as an adjuvant therapy
- CDK 4/6 inhibitor approved for HER2-positive ABC
- Tamoxifen
- BEC 58 inhibitor approved for ER/HER2+ ABC

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Use of Intrinsic gene set clearly defines distinct subtypes of breast cancer with unique biologies

But within each subgroup does not give robust predictive information

Sorlie et al PNAS 2003

TNBC subtypes

Lehmann et al JCI 2011

Commercial Genomic Assays

- Mammaprint
- Rotterdam Signatures
- Genomic Grade Index
- IHC4
- Oncotype Dx Recurrence Score
- Breast Cancer Index
- Prosigna PAM50
- EndoPredict

And the list is growing

Prognostic score of DCIS

The MINDACT study design

The primary analysis population

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The primary analysis population

Clinical outcome of the MINDACT population at 5y median follow-up

B) DISCORDANT RISK GROUPS: PRIMARY TEST

The primary analysis population

The primary statistical test

DMFS at 5Y

Null Hypothesis: set at 92%

Observed 5Y DMFS = 94.7%

95% CI ≈ 92.5 – 96.2% excludes 92% !!!

Efficacy: CT vs no CT in discordant risk groups

Intent-to-treat analysis

Oncotype Dx and Chemotherapy Benefit

Results from TAILORx and Conclusions

- Genomic Assays are prognostic of a group of patients with very low risk of recurrence
- In this group of patients the addition of chemotherapy is unlikely to be of benefit.

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I-SPY2 Update

<table>
<thead>
<tr>
<th>Veliparib-carbo</th>
<th>Control</th>
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</thead>
<tbody>
<tr>
<td>BRCA+ 12 (17%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>BRCA- 39 (54%)</td>
<td>21 (48%)</td>
</tr>
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</table>

Combination of veliparib and carboplatin may be beneficial BUT larger number of BRCA+ pts

Biomarker performance within TN subset

3 gene expression signatures relating to DNA damage repair deficiency

- PARP1
  - 3 gene DNA repair deficiency signature: BRCA1, CHEK2, MRE11A, NBN, XPA.
  - 3% overlap of PARP1 and BRCA2/1344
- BRCAgene
  - 77 gene BRCA1/2 deficiency signature.
- MammaPrint High1/High2 (MP1/2) classification
  - Further stratification of prognosis: MP1-high risk (PMID:22337374)

Nearly all of the specific sensitivity to veliparib/carboplatin is in the 40% of TN patients positive for BOTH sensitivity markers.

AR-Driven Biology in Patients

- Measured via flow cytometry
- Harsh AR secretion
- Defining in vitro AR activity
- Phenotypic and genotypic AR profiles
- AR activation in cell lines
- AR-regulated gene expression

Study Schema (MDV3100-11)

Statistical considerations:
- 0.05 alpha level, 80% power against 1% of alternative hypothesis, alpha = 0.05

PFS in Evaluable and ITT Populations

Presented by Tiffany Traina at 2015 ASCO Annual Meeting

AR-Driven Biology in Patients

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Presented by Tiffany Traina at 2015 ASCO Annual Meeting

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Increased HER2 expression in tamoxifen-treated breast cancers

<table>
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<tr>
<th></th>
<th>At diagnosis</th>
<th>At recurrence</th>
<th>p</th>
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<tbody>
<tr>
<td>ER</td>
<td>79%</td>
<td>59%</td>
<td>0.035</td>
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<tr>
<td>PR</td>
<td>34%</td>
<td>22%</td>
<td>0.13</td>
</tr>
<tr>
<td>HER2/neu (2+, 3+)</td>
<td>27%</td>
<td>53%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Suggests hormone-refractory phenotype is associated with incremental decreases in hormone receptors and increases in HER2.

Whole exome and transcriptome sequencing of resistant ER+ metastatic breast cancer

**Kaklamani et al Biomarkers 2010 15(2):191-3**

**Acquired ESR1 Mutations in ER+ MBC**

**Acquired HER2 Mutations in ER+ MBC**

**Acquired RB1 loss in ER+ MBC**

**Acquired PI3K pathway mutations are observed in ER+ MBC – including: PTEN, PIK3CA, and AKT1**

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This presentation is the intellectual property of the author/presenter. Contact them at (kaklamani@uthscsa.edu) for permission to reprint and/or distribute.
• Two phase III clinical trials:
  • SOFEA – fulvestrant vs exemestane +/- aromidex n=162
  • Paloma3 – fulvestrant +/- palbociclib n=360
• Hypothesis – ESR1 mutations would do better on fulvestrant vs AI
• Further improvement with addition of palbociclib

ESR1 mutations were present 39.1%, polyclonal in 46%
Detection of ESR1 mutations will influence your next choice of endocrine therapy

TNBC, n=32
PDL1+ in stroma or in ≥1% of tumor cells (>58% of TNBC screened)
Overall response rate 18.5%
ongoing phase 2 study (KEYNOTE-086 trial)

PD-1/PD-L1 Blockade in Breast Cancer

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Target</th>
<th>Subtype</th>
<th>Patients</th>
<th>ORR</th>
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<tbody>
<tr>
<td>Avelumab</td>
<td>PD-L1</td>
<td>All</td>
<td>168</td>
<td>4.8%</td>
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<tr>
<td></td>
<td>PD-1+</td>
<td>All</td>
<td>12</td>
<td>33.3%</td>
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<tr>
<td>Pembrolizumab</td>
<td>PD-L1+</td>
<td>TNBC</td>
<td>58</td>
<td>8.6%</td>
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<tr>
<td></td>
<td>PD-L1+</td>
<td>TNBC</td>
<td>9</td>
<td>44.4%</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PD-L1+</td>
<td>ER+HER-2</td>
<td>20</td>
<td>18.5%</td>
</tr>
<tr>
<td></td>
<td>PD-L1+</td>
<td>TNBC</td>
<td>21</td>
<td>19%</td>
</tr>
</tbody>
</table>

Emens LA et al, AACR 2015
Rugo et al SABCS 2015
Nanda R et al JCO 2016;34:2460

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Conclusions

- We have come a long way from Dr Beatson’s observation
- Adjuvant chemotherapy can be selected based on tumor genomic profile
- HRD assay predicting sensitivity to platinum
- AR genomic assay predicting response to enzalutamide
- Tumors evolve
- Several actionable mutations such as PIK3CA, ESR1 changing the landscape of treatment
- Still unclear what markers to use for immunotherapy