ILC Symposium: highlights on translational research

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Outline

• What is translational research?
• How can models be translated into the clinic?
• Prognostic tests for ILC
• Disease heterogeneity
• Towards new treatment targets
• Autopsy programs to enhance research
What is translational research?

Fundamental research = Scientists using different models to understand the underlying mechanisms of a disease

Translational research = Researchers that bring the knowledge of the fundamental research into the clinic

Clinical research = Trials with patient data and trials with new types of medication
How can models be translated into the clinic?
Differences in the animal kingdom

• Unique differences in the mammary gland of different species
  • Some species adapt their milk to the sex of the baby
  • Others adapt in to the age of the babies
Similarities with animal models

- The mammary gland of the mouse shows some similar features as compared to the human mammary gland
  - Branching pattern in the breast
  - The build-up of the cells of the branches in the breast

- Mouse models can help understand how human breast tumors grow and spread
Prognostic tests for ILC
What is a prognostic test?

- Tests of different mutations that can occur in the genes of the tumor to determine how aggressive the tumor is
  - Gene signatures of the tumors
- Determine which patient are at high risk of developing distant tumor growths (=metastases) in the future
- Used in the clinic to determine if additional treatment with chemotherapy is necessary in patients where it is not clear
- Mammaprint, OncotypeDx, Prosigna, ...
Prognostic tests for ILC

• Breast Cancer Index
  • Can be used in patients with ILC
  • Determines which patients are at risk for early and late distant recurrences (= metastases)

• Lobsig
  • Prognostic tests specifically developed for patients with ILC
  • Promising results for determining which patients are at high risk for recurrences ⇒ needs validation

ARTICLE OPEN
LobSig is a multigene predictor of outcome in invasive lobular carcinoma

Amy E. McCart Reed, Samir Lai, Jamie R. Kutatsovic, Leesa Wodner, Alan Robertson, Xavier M. de Luca, Priyadi Kalita-de Croft, Andrew J. Dailey, Craig P. Cooney, Liya Kuo, Katrin Ferguson, Colleen Nolands, Gregory Miller, Julie Johnson, Lynne E. Reid, Renique Males, Jodi M. Saarinen, Georgia Gheveria-Trench, Lachlan Conlin, Sunil R. Lakhani and Peter T. Simpson

June 2019
Disease heterogeneity
What is disease heterogeneity?

• Variations in different aspects of the tumor
  • Expression of receptors
    • e.g. hormone sensitive or not
  • Mistakes in the genes of the tumor cells (= mutations)
  • Other cells that close to the tumor and that can influence the tumor (= tumor microenvironment)
  • ...

• Large differences in these aspects between ILC and non-special breast cancer underpin the need to see ILC as a separate disease
Differences in mutations

- Comparison between ILC and NST
  - Luminal A = hormone sensitive, HER2 negative
  - Double scale
    - Percentage of ILC with those specific mutations = horizontal
      - The more to the right a gene is put, the more mutations in that gene in ILC
    - Percentage of NST with those specific mutations = vertical
      - The higher a gene is put, the more mutations in that gene in NST

Heterogeneity of E-cadherin and the immune microenvironment in ILC
Rachel Natrajan
Differences in immune cells in the tumor microenvironment

- Lymphocytes = type of white blood cells
  - Involved in the immune response
  - TILs = Tumor infiltrating lymphocytes
    - Lymphocytes nearby the tumor cells
    - Although normally part of the body’s defence system, cancer cells can inactivate and exhaust the immune cells
      \[\implies\] higher TILs in hormone sensitive tumors is a sign of more aggressive tumors
  - TILs are lower in ILC

Heterogeneity of E-cadherin and the immune microenvironment in ILC
Rachel Natrajan
Towards new treatment targets
ROS1-inhibitors

• Most ILC have a mutation in CDH1-gene

Keynote
Steffi Oestenreich

HER2 mutations

• HER2 is a protein that can be overly expressed on a tumor cell (=amplification)
• The underlying gene can also be mutated (even without amplification)
• More often in metastatic breast cancer
• More common in ILC than NST
• Those mutations can be targeted by new drugs like neratinib
Autopsy programs to enhance research
Autopsy programs to enhance research

• Currently 2 autopsy projects that are including also ILC

<table>
<thead>
<tr>
<th>Pittsburgh: Hopes for Others</th>
<th>Leuven: UPTIDER</th>
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<tbody>
<tr>
<td>24 autopsies performed</td>
<td>16 autopsies performed</td>
</tr>
<tr>
<td>21 more consented</td>
<td>5 more consented</td>
</tr>
<tr>
<td>1 ILC, 1 mixed ILC/IDC</td>
<td>3 ILC, 3 mixed ILC/IDC</td>
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<tr>
<td>6-27 biospecimens/patient</td>
<td>45-303 samples/patient + liquid samples</td>
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<tr>
<td>Duration of 4,2 hours on average</td>
<td>Duration of 6,3 hours on average</td>
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Creation of new models

• Collaboration between the programs

Keynote
Steffi Oestenreich

Enhancing research on metastatic lobular breast cancer through a post-mortem tissue donation study
Karen Van Baelen
Enhancing research on metastatic lobular breast cancer through a post-mortem tissue donation study
Karen Van Baelen
Take home messages
Take home messages

• Translational research is bringing the knowledge of the fundamental research into the clinic
• Mouse models can help understand how human breast tumors grow and spread because of similarities in mouse and human mammary gland
• Prognostic tests are used to determine how high the risk of future metastases are to see if additional treatment is needed
  • New tests are being evaluated for ILC
Take home messages

• New treatments are on their way
  • ROS1 inhibitors: specifically for ILC, since they more often have a CDH1 mutation and cells with this mutation can no longer survive if ROS1 is inactivated
  • HER2 mutations: more common in metastatic ILC, targeted with new drugs
• Autopsy programs can help to understand how ILC spreads and grows
  • 2 autopsy programs ongoing that have substudies on ILC
Thank you for your attention