Highlights of the 2022 Joint International ELBCC/Lobsterpot & LBCA Invasive Lobular Carcinoma (ILC) Symposium

Clinical Highlights

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Clinical Topics from the ILC Symposium

- Epidemiology
- Diagnosis and Treatment
  - Imaging
  - Local Therapy
  - Systemic Therapy
- Early stage and metastatic
Clinical Themes

• Important concepts:
  • Discordance of diagnosis on histopathology
    • Recommendation for E-cadherin staining
  • Reduced sensitivity of imaging
  • Increased rates of mastectomy and axillary dissection
  • A subset of patients with ILC benefit from chemotherapy
  • Targeting Receptor tyrosine kinases in trials
Epidemiology: Breast Cancer Risk Factors

• Early menarche, late menopause, nulliparity, late parity (after age 35)
• Lobular carcinoma in situ
  • increased lifetime risk of breast cancer, all types but relatively more ILC
• Combined estrogen and progesterone hormone replacement therapy
• Obesity in setting of post-menopausal status increases risk of ER positive breast cancer
• Alcohol increases risk of ILC compared to NST (Li et al)
Epidemiology

Summary of risk factors

**Germline Mutations**
- Mutations in BRCA2, PALB2, ATM, CHEK2
- Majority of the 313 breast cancer low risk susceptibility SNPs
- CDH1 mutations
  - (BRCA1 mutations rare)
- More lobular specific rare variants and low risk susceptibility SNPs to be identified?

**Other Risk Factors**
- Post menopausal obesity
- Oral contraceptive
- Later age of menopause
- No / few pregnancies
- Combined HRT use
  - Early age of menarche
  - Later age of first birth
  - Alcohol
- IVF
  - Breast density
  - Ethnicity
  - Smoking

By better understanding the different risk factor profiles of different subtypes of breast cancer, breast cancer prevention can be personalized to individual needs.

Adapted from Van Baelen et al 2022
Polygenic risk score: ILC specific SNP’s

Low-penetrance genetic variants & ILC

- 313 low penetrance single nucleotide polymorphisms (SNPs) that predispose to breast cancer
- Tend to be located in non-coding regions
- Common in the population
- Majority predispose to breast cancer in general or ER+
- Some SNPs are lobular specific
  - rs11977670 on chromosome 7q34
  - rs11249433, at 1p11.2 stronger association with ILC

Elinor Sawyer
Epidemiology

• Identifying those with elevated risk for ILC could guide screening
  • Mammography has lower sensitivity for ILC
    • Lack of desmoplastic reaction, diffuse growth pattern

• The Great Lakes Breast Cancer Consortium
  • 33,662 patients, of which 3,617 have ILC
  • ILC patients diagnosed at later stages
  • Higher rates of mastectomy use in ILC
Diffuse growth pattern impacts stage IV patients as well.

“Unmeasurable” peritoneal involvement of ILC in patient with stage IV disease.

Wong YM et al.11 Infiltrative pattern of metastatic invasive lobular breast carcinoma in the abdomen: a pictorial review
Insights into Imaging volume 12, Article number: 181 (2021)
Need more patients with ILC in clinical trials, especially stage IV

**Trial Enrollment Rates**

Patients with stage IV ILC were significantly underrepresented in clinical trials (two sample test of proportion $p<0.005$)

*Decreased enrollment in breast cancer trials by histologic subtype: does invasive lobular carcinoma resist RECIST? Abell MK et al, npj Breast Cancer 2021*
Endocrine Therapy and ILC

- Retrospective analysis of BIG 1-98
  - Relative difference in AI effect versus tamoxifen significantly larger in ILC
  - Potential for treatment resistance to tamoxifen in ILC
- In pre-menopausal women with ILC and low clinical risk, tamoxifen likely adequate
- In pre-menopausal women with ILC and high clinical risk, optimal endocrine therapy less clear (OFS/AI?)
- Optimal duration of endocrine therapy needs more study
- ILC specific analyses of SOFT and TEXT trials ongoing

Hormone Receptor Function and Drug Responses in ILC: Otto Metzger
Chemotherapy and ILC

• Molecular assays such as Mammaprint and Oncotype Dx are prognostic in ILC
• A higher proportion of ILC is molecularly low risk than IDC
• However, a subset of patients with ILC benefit from chemotherapy
In multivariate analysis, chemotherapy was associated with improved overall survival in patients with node positive ILC with high recurrence score.
Chemotherapy and ILC

What type of adjuvant chemotherapy for ILC?

SUCCESS and PlanB RCT: n=5,924 pts, ±50% N+, 40% grade 3, ILC n=726

In patients with ILC and 4 or more positive nodes, chemotherapy regimens containing anthracycline were associated with significantly improved DFS compared to non-anthracycline containing regimens.

Analysis of SUCCESS and PlanB trials:

In patients with ILC and 4 or more positive nodes, chemotherapy regimens containing anthracycline were associated with significantly improved DFS compared to non-anthracycline containing regimens.

degigorio, Br J Cancer 2022

Toward Precision Medicine for ILC; Sabine Linn
Chemotherapy and ILC

Dose dense adjuvant chemotherapy for ILC?

<table>
<thead>
<tr>
<th>Category</th>
<th>Events/Women</th>
<th>Dose–intense events</th>
<th>Ratio of annual event rates</th>
<th>Ratio (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) Histological type ($\chi^2 = 2.5; 2p &gt; 0.1; NS$)</td>
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<tr>
<td>Ductal</td>
<td>1264/8733</td>
<td>1418/8831</td>
<td>0.88 (0.80 – 0.98)</td>
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<tr>
<td></td>
<td>(19%)</td>
<td>(14%)</td>
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<tr>
<td>Lobular</td>
<td>185/1250</td>
<td>223/1271</td>
<td>0.81 (0.61 – 1.08)</td>
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<td>(14%)</td>
<td>(17%)</td>
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<tr>
<td>Total</td>
<td>2890/18623</td>
<td>200/14315</td>
<td>0.870 (0.826 – 0.916)</td>
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<tr>
<td></td>
<td>(15%)</td>
<td>(17%)</td>
<td>$2p &lt; 0.0001$</td>
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19% relative risk reduction to die from ILC with dose-dense chemotherapy

±2500 ILC patients – RR 0.81 for breast cancer specific survival

EBCTCG, Lancet 2019

Dose dense chemotherapy associated with improved breast cancer specific survival in ILC
Receptor tyrosine kinases in clinical trials

• Several receptor tyrosine kinases have been implicated in ILC and may be targets for therapy
  • ROS1
  • PI3K/AKT/PTEN
  • BET
  • IGF-1R
**E-Cadherin/ROS1 Inhibitor Synthetic Lethality in Breast Cancer**

**Synthetic lethality** arises when a combination of deficiencies in the expression of two or more genes leads to cell death, whereas a deficiency in only one of these genes does not.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Design</th>
<th>Patient population</th>
<th>Nr of pts</th>
<th>Treatment</th>
<th>Primary endpoint</th>
<th>Date expected completion enrolment</th>
</tr>
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<tbody>
<tr>
<td>ROSALINE</td>
<td>2</td>
<td>Single arm</td>
<td>Stage I–III ILC</td>
<td>45</td>
<td>Entrectinib + letrozole (+goserelin)</td>
<td>RCB</td>
<td>October 2022</td>
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<tr>
<td>(NCT04551495)</td>
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<tr>
<td>ROLo</td>
<td>2</td>
<td>Single arm</td>
<td>Stage IV E-cadherin negative BC</td>
<td>58</td>
<td>crizotinib + fulvestrant</td>
<td>Response rate</td>
<td>May 2023</td>
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<tr>
<td>(NCT03620643)</td>
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Ongoing trials of ROS1 inhibitors based on synthetic lethality data.
As of yet targeting these pathways shows only modest response and can cause toxicity but still of interest as treatment target.

- Potentially test AKT inhibition in combination with IGF1R inhibitor (MEK inhibitor).

Growth factor signals are hyperactivated upon E-cadherin loss, independent of somatic activating mutations in downstream effectors.

Potential for drugs targeting the PI3K/Akt axis in ILC, irrespective of oncogenic pathway mutations.
Conclusions

• Traditional risk factors for breast cancer remain
  • Working towards ILC specific predictors

• Decreased sensitivity of imaging
  • Leads to delay in diagnosis
  • Difficulty with surgical planning and need for more extensive operations
  • Challenges in following disease extent could impact clinical trial enrollment
Conclusions

• Systemic therapy
  • Potentially tamoxifen resistance in some ILC → ongoing work
  • Chemotherapy is beneficial in some ILC
    • Clinically high risk, 4 or more positive nodes → dose dense anthracycline containing regimen
    • Targeted therapies being tested

• Increasing lobular specific analysis of trial data, development of lobular consortia