"Window of opportunity" studies: Biologic opportunities and ethical issues

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St Louis
Different Window Designs

Therapeutic Intent (months)

No Therapeutic Intent (days to weeks)
Why conduct “window studies”? 

• Demonstrate that potential chemoprevention agents have relevant biological effects against tumor cells 
• Identify tumor resistance or sensitivity profiles to targeted agents 
• Demonstrate a biological agent has expected mechanism of action 
• Establishing “biologically effective dose”
Practical constraints for “no therapeutic intent” window studies

- Ethical and practical difficulties of conducting studies when there is no expected patient benefit
- Restricted to “non-toxic” agents with a very well established toxicity profile
- Logistics of sample collection and consent
- Relies on robust “surrogate endpoints” for clinical events or relevant biological effects
- Surgical setting may present special difficulties with certain agents
Examples of agents assessed in window studies

- Endocrine agents with low short term toxicity
- Dietary components
- Commonly used drugs with “incidental anticancer activity” (COX2 inhibitors and statins)
- Signal transduction inhibitors with a very well established toxicity profile
Why conduct “window studies”? 

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Perillyl Alcohol Window study

All patients screened
N = 267

Reasons for non-participation
N = 230

Stearns et al, Clinical Cancer Research, 10: 7583-7591, 2004
Ethical Issues

• Potential for patient harm in the early disease setting
• Discussion of research with patients who are experiencing a high level of distress due to a recent diagnosis of breast cancer
• May interfere with subsequent clinical trial accrual
## Paired Samples
(no dedicated tissue accrual)

<table>
<thead>
<tr>
<th>Type of lesion on biopsy</th>
<th>Number of patients</th>
<th>% times lesion the same</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDC</td>
<td>26</td>
<td>15 (58%)</td>
</tr>
<tr>
<td>ILC</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>IDC/ILC</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>DCIS</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Atypical Medullary</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>ALL</td>
<td>36</td>
<td>20 (56%)</td>
</tr>
</tbody>
</table>

Dedicated frozen tissue acquisition

<table>
<thead>
<tr>
<th>T Stage</th>
<th>N</th>
<th># Cores/pat</th>
<th>Ave # Cores &gt; 60% cancer</th>
<th># patients with a 60% cancer core</th>
<th># patients with any cancer in core</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0 (DCIS)</td>
<td>11</td>
<td>3.5</td>
<td>0.0</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>T1</td>
<td>85</td>
<td>3.8</td>
<td>1.2</td>
<td>49</td>
<td>70</td>
</tr>
<tr>
<td>T2</td>
<td>40</td>
<td>5.1</td>
<td>2.0</td>
<td>31</td>
<td>40</td>
</tr>
<tr>
<td>T3</td>
<td>8</td>
<td>5.0</td>
<td>2.3</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>T4</td>
<td>6</td>
<td>3.0</td>
<td>1.0</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Clinically Applicable Frozen Tumor Tissue Collection and Gene Expression-Based Predictions of Breast Cancer Phenotypes Tebbit et al, submitted
Options to improve Tissue Acquisition at surgery

Obtain extra samples during diagnostic radiology

Dedicated device to obtain samples at lumpectomy

Clinically Applicable Frozen Tumor Tissue Collection and Gene Expression-Based Predictions of Breast Cancer Phenotypes Tebbit et al, submitted
Dedicated frozen tissue acquisition

<table>
<thead>
<tr>
<th>Biopsy Device</th>
<th>N</th>
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<tbody>
<tr>
<td>YES</td>
<td>18</td>
<td>6.2</td>
<td>2.3</td>
<td>15 P=0.001</td>
<td>17 P=0.37</td>
</tr>
<tr>
<td>NO</td>
<td>75</td>
<td>4.9</td>
<td>1.7</td>
<td>19</td>
<td>53</td>
</tr>
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Clinically Applicable Frozen Tumor Tissue Collection and Gene Expression-Based Predictions of Breast Cancer Phenotypes Tebbitt et al, submitted
Why conduct “window studies?”

- Demonstrate that potential chemoprevention agents have relevant biological effects against tumor cells
- **Identify** tumor resistance or sensitivity profiles
- Demonstrate a biological agent has expected mechanism of action
- Establishing “biologically effective dose”
## Ki67 is a PD biomarker

<table>
<thead>
<tr>
<th></th>
<th>Mammography Response Cases (%)</th>
<th>Clinical Response Cases (%)</th>
<th>Ki67 Response Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Letrozole</strong></td>
<td>32/79 (40.5)</td>
<td>56/79 (70.9)</td>
<td>54/78 (69.2)</td>
</tr>
<tr>
<td><strong>Tamoxifen</strong></td>
<td>21/90 (23.3)</td>
<td>45/90 (50.0)</td>
<td>35/88 (39.8)</td>
</tr>
<tr>
<td>**P value ***</td>
<td>0.0167</td>
<td>0.0059</td>
<td>0.0002</td>
</tr>
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*Mantel-Haenszel for L versus T

Tao, Y et al J Steroid Biochem Mol Biol 95:91-5, 2005
**Effect of Letrozole on Proliferation by HER2 Status**

<table>
<thead>
<tr>
<th></th>
<th>HER2 FISH+</th>
<th>HER2 FISH-</th>
<th>Total</th>
<th>Fisher</th>
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<tr>
<td>Cell cycle CR -</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>111</td>
<td>113</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>15</td>
<td>73</td>
<td>88</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>184</td>
<td>201</td>
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PO24 letrozole arm combined with Edinburgh letrozole audit series.
DFS: ER+/HER2 by Treatment

Tamoxifen

% Alive and disease-free

0 1 2 3 4 Years

ER+/HER2- (n=1986)

ER+/HER2+ (n=107)

HR=0.52 (0.31, 0.88)

Letrozole

% Alive and disease-free

0 1 2 3 4 Years

ER+/HER2- (n=1985)

ER+/HER2+ (n=127)

HR=0.56 (0.31, 0.98)

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Correlative Science Approach

Ki67 analysis
Agilent whole genome 44K chip
Agilent 244K array CGH
Gene Resequencing
IHC with phosphoprotein-specific antibodies

Aromatase Inhibitor Therapy

Ki67 analysis
IHC with phosphoprotein-specific antibodies
Tumor response
Array Comparative Genomic Hybridization

Sample size
ACOSOG Z1031

Postmenopausal ER Allred 6-8 Clinical stage 2 and 3

- Exemestane
- Letrozole
- Anastrozole

Accrual 78/375

Continued therapy with an AI where possible; radiotherapy chemotherapy discretionary

PI M.J. Ellis.
Status Active: http://www.ctsu.org/.
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VICC BRE0222: EGFR inhibitor erlotinib in untreated operable breast cancer

Is there a biomarker that can identify breast cancers in which the EGFR inhibitor reduces proliferation and that can, thus, be used for patient selection into trials with these drugs?

Arteaga, C Preliminary data
Erlotinib inhibits EGFR phosphorylation in treatment-naive breast cancers

Arteaga, C Preliminary data
Erlotinib inhibits HER2 phosphorylation in treatment-naive breast cancers

Arteaga, C Preliminary data
Erlotinib inhibits proliferation of breast cancer cells in primary tumors

70%*

* % Ki67+ cells

Arteaga, C Preliminary data
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"Phase 0" clinical trials

OPINION

Compressing drug development timelines in oncology using phase ‘0’ trials

Shivaani Kummar, Robert Kinders, Larry Rubinstein, Ralph E. Parchment, Anthony J. Mergo, Jerry Collins, Oxana Pikerai, Jennifer Low, Seth M. Steinberg, Martin Gutierrez, Sherry Yang, Lee Helman, Robert Wiltrout, Joseph E. Tomaszewski and James H. Doroshow

Desirable Biomarker Characteristics

- Accuracy
- Dynamic range
- Precision
- Reproducibility
- Robustness
- Sensitivity

Phase 0 clinical trial (advanced disease)

Conclusions

- Window of opportunity studies are feasible but remain challenging
- Clinical barriers are determined by the intent of the study, the nature of the agent and the sample size
- Scientific barriers are determined by the quality of the biomarker analysis and the mechanism of action of the agent