Breast cancer molecular subsets, response marker discovery and clinical trials

Lajos Pusztai M.D., D.Phil.
Department of Breast Medical Oncology

Two points

- Future breast cancer studies should be subtype-specific.
- Candidate response markers to new (and old) drugs can be studied prospectively using marker-directed phase II trial designs with early stopping rules.

Breast cancer subtypes

Imagine a gastrointestinal cancer study where all types of GI cancers are eligible for treatment.

After completion of the study, subset analysis is performed for colon, rectal, gastric, and esophageal tumor locations.

Why not include all types of breast cancers in future studies as we used to do?

- ER+, TNBC and HER2 positive cancers respond differently to various therapies
  - chemo, endocrine, trastuzumab
- Composite survival curves can be confusing and unstable.
  - Variable proportion of patients in subsets x variable efficacy of therapies in each subset
- Prognostic and response markers can be (and most that we currently have are) breast cancer subtype-specific.

Impact of Recurrence Score subsets on survival and power of randomized trials

<table>
<thead>
<tr>
<th>Recurrence Score (RS)</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS-L</td>
<td>40%</td>
<td>20%</td>
</tr>
<tr>
<td>RS-I</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td>RS-H</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td>HR</td>
<td>1.33</td>
<td>1.26</td>
</tr>
<tr>
<td>Power</td>
<td>80%</td>
<td>60%</td>
</tr>
</tbody>
</table>

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Different chemotherapy sensitivity according to ER and HER2 status in neoadjuvant studies

Table 4. Pathology, complete response according to HER2 and ER expression

<table>
<thead>
<tr>
<th>Overall population (n = 336)</th>
<th>HER2-positive (n = 138)</th>
<th>HER2-negative (n = 200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER-positive subgroup (n = 207)</td>
<td>72% (95% CI: 64-80)</td>
<td>53% (95% CI: 44-64)</td>
</tr>
<tr>
<td>ER-negative subgroup (n = 129)</td>
<td>71% (95% CI: 62-79)</td>
<td>62% (95% CI: 54-71)</td>
</tr>
</tbody>
</table>

ER-positive, HER2-positive patients are almost as sensitive to chemotherapy as ER-patients, in general.

Proportion of patients in different RS categories in 6 studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Low Risk (RS &lt; 18)</th>
<th>Int. Risk (RS 18-30)</th>
<th>High Risk (RS ≥ 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B14*</td>
<td>51%</td>
<td>22%</td>
<td>27%</td>
</tr>
<tr>
<td>NSABP B20*</td>
<td>54%</td>
<td>21%</td>
<td>25%</td>
</tr>
<tr>
<td>Kaiser controls*</td>
<td>56%</td>
<td>19%</td>
<td>25%</td>
</tr>
<tr>
<td>ECOG 2197**</td>
<td>49%</td>
<td>31%</td>
<td>29%</td>
</tr>
<tr>
<td>SWOG 8814***</td>
<td>40%</td>
<td>28%</td>
<td>32%</td>
</tr>
<tr>
<td>ATAC</td>
<td>59% (LN-)</td>
<td>26% (LN-)</td>
<td>15% (LN-)</td>
</tr>
</tbody>
</table>

Prognostic and response markers can be breast cancer subtype-specific.

- Histological grade is prognostic (and predictive of chemo response) among ER+ cancers, weak or not prognostic in ER- cancers, most ER-negative cancers are high high grade!
- OncotypeDX prognostic (+/- TAM) in ER+ cases but not useful in ER-, almost all ER- cases are high risk RS>31!
- MammaPrint prognostic in ER+, not useful in ER-, almost all ER- cases are high risk!
- Proliferation Score (signature) prognostic/predictive in ER+ cancers but not among ER-, tend to have higher scores.
- Tau-expression, prognostic/predictive in ER+, not useful in ER- cancer all tend to have low Tau expression.

Candidate response markers have to be validated before they can be used for patient selection in a clinical trial

- This is an oximoron
- Imagine that we can only conduct a phase II study if the drug is already known to be effective in patients!

We conduct the clinical trials to find out if a drug is effective or not.

It is entirely reasonable to do same for a response marker

Tandem, 2-step Phase II trial design to rapidly evaluate a priori defined candidate predictive markers in the clinic

“Tandem 2-step phase II trial”

1. Mechanism of action
2. Preclinical models
3. Retrospective analysis

Assay must be fully defined and IDE is required


Statistical considerations

1. Define early stopping rules:

   Targeted level of activity is 25% clinical benefit (CB) rate. We feel comfortable stopping the trial early if it becomes apparent that there is < 7.5% chance that this level of activity is achieved. The early stopping boundaries are:

   - Probability of early termination is 80% if the true CB rate is 10%, and it is 7.5% if the CB rate is 25%.

   - If the true CB rate is 25% with a maximum sample size of N=50, the observed CB rates would fall between 17% and 36%, 90% of the time.

2. Maximum sample size calculations:

   Sample size is defined by minimum CB rate and 90% credible interval:

   - Sample size: 40
   - Lower bound of CB rate: 0.16
   - Upper bound of CB rate: 0.38

   If the true CB rate is 25% with a maximum sample size of N=50, the observed CB rates would fall between 17% and 36%, 90% of the time.
Candidate predictors for dasatinib

1. Dasatinib inhibits at least 19 different protein kinases with high affinity (BCR-ABL, ERK, SRC, PDGFR, KIT, FYN, YES, etc.). Dasatinib target index can be calculated as the weighted average expression of all targets (where the weight is the inhibitory concentration).

2. Src activation pathway consisting of 73 genes was reported. Compared HMEC cells versus Src-transformed HMEC (Bild et al., Nature 439:353-7, 2006).

3. BMS has developed candidate dasatinib response predictor from in vitro data. Compared dasatinib-resistant versus sensitive cell lines (F Huang et al., Cancer Res 2007).

Overlap of response prediction for the 3 different predictors in human breast cancer data.

Advantages of the tandem, 2-step, Phase-II trial design

- Estimates response rates in both unselected and selected patient populations.
- Multiple predictors for the same drug can be assessed simultaneously in the same study.
- It efficiently discards candidate markers with low PPV and identifies promising markers for further validation (it also gives an idea about marker prevalence).
- Eliminates IRB obstacles for obtaining biopsies.
- Creates a unique and currently missing tissue resource.

Disadvantage
- The predictor must be fully defined a priori with cut offs and performed in CLIA environment with IDE from the FDA.

Conclusions

- Future breast cancer studies may be performed separately for at least the 3 major phenotypic groups (ER+, HER2-, TNBC).
  - For ER+ cancers stratification by one of the existing molecular prognostic assays will be important in order to interpret trial results.
- Candidate response markers to new (and old) drugs can be studied prospectively using marker-directed phase II trial designs with early stopping rules.

A potential synthesis of these ideas