A statistical approach for personalized medicine and benefit / risk assessment

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Limitations of current analyses of clinical trials

• A single (« primary ») endpoint drives decision-making

• Composite endpoints consider time to first event, instead of time to most relevant endpoint

• « Secondary » endpoints are analyzed descriptively

• Safety is informally balanced against efficacy, resulting in debatable risk / benefit analyses

• Patient preferences are not formally taken into account
OXALIPLATIN IN COLORECTAL CANCER
Leucovorin and Fluorouracil With or Without Oxaliplatin as First-Line Treatment in Advanced Colorectal Cancer


**Conclusion:** The LV5FU2-oxaliplatin combination seems beneficial as first-line therapy in advanced colorectal cancer, demonstrating a prolonged progression-free survival with acceptable tolerability and maintenance of QoL.

Advanced colorectal cancer

420 subjects with previously untreated metastatic colorectal cancer

210

LV5FU2 + oxaliplatin

new combination of 5-fluorouracil, leucovorin and oxaliplatin

210

LV5FU2

standard regimen of 5-fluorouracil and leucovorin

until disease progression, intolerance to treatment, or death
Progression-free survival

HR = 0.66, P = 0.0003

Survival

Overall Survival

LV5FU2+oxaliplatin (n=210)
LV5FU2 (n=210)

HR = 0.83, P = 0.12

PROBLEMS?
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2. Neither endpoint is perfect:
   - PFS not confounded by further line treatments, less affected by non-cancer deaths, and has more events.
   - OS clinically most relevant and measured without bias or error.
Problems?

1. The two endpoints (OS and PFS) are analyzed separately. PFS reached statistical significance, OS did not.

2. Neither endpoint is perfect:
   - PFS not confounded by other treatments, less affected by non-cancer deaths, and has more events.
   - OS clinically most relevant and measured without bias or error.

3. PFS ignores the time between progression and death. The time to first event ignores subsequent events. LV5FU2 + oxaliplatin might prolong PFS, but shorten OS afterwards.
A DIFFERENT APPROACH
A new method of analysis...

Generalized pairwise comparisons:

- Compare every patient in the treated group with every patient in the control group

- Each pair may favor treatment, control, or neither in terms of several prioritized outcomes (OS first priority, TTP second)

- This approach naturally leads to the « net treatment effect »

ALL PAIRWISE COMPARISONS (36)
TREATMENT GROUP

Survival times
3
5+
6
9+
11+
12

CONTROL GROUP

Survival times
1
3
3
7+
9
9+

ALL PAIRWISE COMPARISONS (36)
TREATMENT BETTER
(19 PAIRS)
TREATMENT GROUP

CONTROL GROUP

CONTROL BETTER
(6 PAIRS)
TREATMENT GROUP

UNINFORMATIVE PAIRS:

TIES
(2 PAIRS)

CONTROL GROUP
UNINFORMATIVE PAIRS:
CENSORING
(9 PAIRS)
19 PAIRS FAVOR TREATMENT
6 PAIRS FAVOR CONTROL
11 PAIRS ARE UNINFORMATIVE
A general measure of treatment effect

Consider a generalization of the Wilcoxon-Mann-Whitney $U$-statistic

$$U_{ij} = \begin{cases} 
+1 & \text{if } (X_i, Y_j) \text{ pair is favorable} \\
-1 & \text{if } (X_i, Y_j) \text{ pair is unfavorable} \\
0 & \text{otherwise} 
\end{cases}$$

$$U = \frac{1}{m \cdot n} \sum_{i=1}^{n} \sum_{j=1}^{m} U_{ij}$$

$U$ is the difference between the proportion of favorable pairs and the proportion of unfavorable pairs. We call this general measure of treatment effect the « net benefit » ($\Delta$).

Pocock et al. proposed a similar (relative) measure of treatment effect called the « win ratio ».

Net benefit (Δ)

For a binary variable, \( \Delta \) is equal to the difference in proportions

\[
\Delta = p_T - p_C
\]

For a continuous variable, \( \Delta \) is related to the effect size \( d \)

\[
\Delta = 2 \cdot \Phi\left(\frac{d}{\sqrt{2}}\right) - 1
\]

For a time-to-event variable, \( \Delta \) is related to the hazard ratio \( \lambda \) and the proportion of informative pairs \( f \)

\[
\Delta = f \cdot \frac{1 - \lambda}{1 + \lambda}
\]

Net benefit (Δ)

Δ is a linear transformation of Harrell’s c-index (or probabilistic index)

\[ U = \Delta = 2 \cdot P(X > Y) - 1 \]

<table>
<thead>
<tr>
<th>Situation</th>
<th>P(X &gt; Y)</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>T uniformly worse than C</td>
<td>0</td>
<td>−1</td>
</tr>
<tr>
<td>T no different from C</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>T uniformly better than C</td>
<td>1</td>
<td>+1</td>
</tr>
</tbody>
</table>
BACK TO OXALIPLATIN IN COLORECTAL TRIAL
## Prioritized outcomes

<table>
<thead>
<tr>
<th>Priority</th>
<th>Outcome</th>
<th>Threshold of clinical relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OS</td>
<td>12 months</td>
</tr>
<tr>
<td>2</td>
<td>OS</td>
<td>6 months</td>
</tr>
<tr>
<td>3</td>
<td>OS</td>
<td>0 month</td>
</tr>
</tbody>
</table>
## Prioritized outcomes

<table>
<thead>
<tr>
<th>Priority</th>
<th>Outcome</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OS</td>
<td>Time to death from any cause</td>
</tr>
<tr>
<td>2</td>
<td>TTP</td>
<td>Time to progression of disease</td>
</tr>
<tr>
<td>OS</td>
<td>TTP</td>
<td>TREATMENT GROUP</td>
</tr>
<tr>
<td>----</td>
<td>-----</td>
<td>----------------</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td><img src="image1.png" alt="Red Icon" /></td>
</tr>
<tr>
<td>5+</td>
<td>4</td>
<td><img src="image2.png" alt="Red Icon" /></td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td><img src="image3.png" alt="Red Icon" /></td>
</tr>
<tr>
<td>9+</td>
<td>6</td>
<td><img src="image4.png" alt="Red Icon" /></td>
</tr>
<tr>
<td>11+</td>
<td>11+</td>
<td><img src="image5.png" alt="Red Icon" /></td>
</tr>
<tr>
<td>12</td>
<td>12</td>
<td><img src="image6.png" alt="Red Icon" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OS</th>
<th>TTP</th>
<th>CONTROL GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td><img src="image7.png" alt="Blue Icon" /></td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td><img src="image8.png" alt="Blue Icon" /></td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td><img src="image9.png" alt="Blue Icon" /></td>
</tr>
<tr>
<td>7+</td>
<td>5</td>
<td><img src="image10.png" alt="Blue Icon" /></td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td><img src="image11.png" alt="Blue Icon" /></td>
</tr>
<tr>
<td>9+</td>
<td>6</td>
<td><img src="image12.png" alt="Blue Icon" /></td>
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</tbody>
</table>

**11 UNINFORMATIVE PAIRS**
1 UNINFORMATIVE PAIR
# Prioritized outcomes

**GENERALIZED PAIRWISE COMPARISONS**  
*(210 \times 210 = 44,100 pairs)*

<table>
<thead>
<tr>
<th>Difference in</th>
<th>Oxliplatin better</th>
<th>Standard better</th>
<th>( \Delta )</th>
<th>Cumulative ( \Delta )</th>
<th>( P )-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>42.6%</td>
<td>32.5%</td>
<td>10.1%</td>
<td>10.1%</td>
<td>0.050</td>
</tr>
<tr>
<td>TTP</td>
<td>9.1%</td>
<td>4.4%</td>
<td>4.7%</td>
<td>14.8%</td>
<td>0.0054</td>
</tr>
</tbody>
</table>

* Unadjusted for multiplicity
CONCLUSIONS
• Generalized pairwise comparisons provide a versatile and powerful analysis method when multiple prioritized outcomes are of interest.

• The net benefit ($\Delta$) is a measure of overall treatment effect (benefit / risk) that has direct clinical meaning.

• The priority of outcomes can be patient-dependent.
References


