The “Net Benefit” and the correlation between benefits and harms

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Problem

Benefit / risk assessments use *marginal* estimates that do not account for the correlation between the outcomes (benefits / risks)

Positive correlation

*Example*: skin rash in patients with EGFR-mutated advanced lung cancer receiving inhibitors of EGFR

No correlation

*Example*: cardiac toxicity in frail patients with advanced breast receiving anthracyclines

Negative correlation

*Example*: toxicities leading to treatment stop in enzyme-deficient patients with advanced colorectal cancer receiving irinotecan

Ref: Buyse et al. J Clin Epidemiol 2021
Pairwise Comparisons

TREATMENT GROUP

CONTROL GROUP

Pairwise comparison

\[ \begin{align*}
X_i & > Y_j \quad \text{(WIN)} \\
X_i & < Y_j \quad \text{(LOSS)} \\
X_i & = Y_j \quad \text{(TIE)} \\
\text{or} \quad X_i & \text{ or } Y_j \text{ missing} \quad \text{(uninformative)}
\end{align*} \]

WINS \quad X_i > Y_j

LOSSES \quad X_i < Y_j

TIES \quad X_i = Y_j

(UNINFORMATIVE)

Ref: Buyse. Stat Med 2010
All Pairwise Comparisons

Ref: Buyse. Stat Med 2010
Net Benefit

\[ \text{Net Benefit} = \frac{\#\text{Wins}}{\#\text{Pairs}} - \frac{\#\text{Losses}}{\#\text{Pairs}} \]

\[ = 2\theta - 1 \]

where \( \theta \) is the « probabilistic index »

\[-1 < \text{Net Benefit} < 1\]

\text{Net Benefit} : \text{probability that a random patient receiving Treatment does better than a random patient receiving Control, minus the probability of the opposite situation}

Ref: Buyse. Stat Med 2010
Win Ratio

Win Ratio = \frac{\#\text{Wins}}{\#\text{Losses}}

0 < \text{Win Ratio} < \infty

Ref: Pocock et al. Eur Heart J 2012
Win Odds

\[ \text{Win Odds} = \frac{\#\text{Wins} + \#\text{Ties}/2}{\#\text{Losses} + \#\text{Ties}/2} \]

\[ = \frac{\theta}{1-\theta} \]

\[ 0 < \text{Win Odds} < \infty \]

Ref: Brunner et al. Stat Med 2021
The Net Benefit is a U-statistic

\[ X_i \ (i = 1, \ldots, m) \]
\[ Y_j \ (j = 1, \ldots, n) \]

\[ u_{ij} = \begin{cases} 
+1 & \text{if } (X_i, Y_j) \text{ pair is a win} \\
-1 & \text{if } (X_i, Y_j) \text{ pair is a loss} \\
0 & \text{otherwise} 
\end{cases} \]

\[ U = \frac{1}{mn} \sum_{i=1}^{m} \sum_{j=1}^{n} u_{ij} \]

\( U \), the Net Benefit, is unbiased and efficient in situations of practical interest

Ref: Verbeeck et al. SMMR 2021
GENERALIZATIONS
1 - Thresholds of Clinical Relevance

Ref: Buyse. Stat Med 2010
GENERALIZATIONS
2 – Outcomes of Any Type

\[ X_i > Y_j \] (WIN)
\[ X_i < Y_j \] (LOSS)
\[ X_i = Y_j \] (TIE)
\[ X_i \text{ or } Y_j \text{ missing} \] (uninformative)

\( X_i > Y_j \) denotes « better outcome »
\( X_i < Y_j \) denotes « worse outcome »

WINS \( X_i > Y_j \)
LOSSES \( X_i < Y_j \)

Ref: Buyse. Stat Med 2010
GENERALIZATIONS
3 – Multiple Prioritized Outcomes

Benefit/Risk Analyses

Erlotinib
569 advanced pancreatic cancers

Gemcitabine + erlotinib: 285
Gemcitabine + placebo: 284

FOLFORINOX
342 advanced pancreatic cancers

FOLFORINOX: 171
Gemcitabine: 171

Nab-Paclitaxel
861 advanced pancreatic cancers

Gemcitabine + nab-paclitaxel: 431
Gemcitabine: 430

Refs: Moore et al. JCO 2007; Conroy et al. NEJM 2011; Von Hoff et al. NEJM 2013
Benefit: Longer OS

- **Erlotinib**
  - HR = 0.82
  - 95% CI (0.69 - 0.99)
  - P = .036
  - Median Survival = 6.37 months

- **FOLFIRINOX**
  - HR = 0.57
  - 95% CI (0.45 - 0.73)
  - P < .001
  - Median Survival = 11.1 months

- **Gemcitabine**
  - Median Survival = 6.8 months

- **Nab-Paclitaxel**
  - Hazard ratio for death, 0.72 (95% CI, 0.62–0.83)
  - P<0.001 by stratified log-rank test
# Risk: Severe Toxicity

<table>
<thead>
<tr>
<th>Worst Toxicity</th>
<th>Erlotinib</th>
<th>Gem</th>
<th>FOLFORINOX</th>
<th>Gem</th>
<th>Gem+NabP</th>
<th>Gem</th>
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<td>24%</td>
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</tbody>
</table>

Clinical Thresholds for OS

Ref: Buyse & Péron, In: Piantadosi & Meinert (eds.), Principles and Practice of Clinical Trials, 2021
Conclusions

The Net Benefit, estimated with Generalized Pairwise Comparisons

– is flexible
– can incorporate multiple prioritized outcomes
– can incorporate thresholds of clinical relevance
– provides a mathematically correct benefit / risk assessment
– is meaningful to patients
Selected References


