Exposure-response in the presence of confounding

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Outline

1. Introduction

2. Example of exposure-response with multiple doses

3. Exposure-response with one dose?

4. Concluding thoughts
Exposure-response is in the mind of the beholder

Ranging across . . .

- PK-PD model
- K-PD model
- PD model driven by a summary measure derived from PK model
- PD model based on observed concentrations
- Dose-response
Introduction

What summary measures?

Some commonly used include:

- $\text{AUC}_{ss}$ (Dose/(CL/F))
- $\text{Caverage}_{ss}$ ($\text{AUC}_{ss}/\tau$)
- $\text{Cmax}$
- $\text{Ctough}$
Why do we need exposure-response analyses?

What do they give us that we can’t learn from dose-response?

- May be closer to mechanism-based models
  - Concentration of drug → biomarker (possibly with a delayed effect)
- May allow more precise estimation when dose-response modeling isn’t informed by the design (e.g., only 2-3 dose levels studied).
- May allow more seamless interpolation (or extrapolation) to doses or populations that weren’t studied
- May allow us to understand if a higher dose is necessary for a subset of patients
(Simulated) Example of E-R with multiple doses

- Phase 2 dose-ranging study
  - 3 treatment groups: placebo, 3, or 5 mg QD
  - n=25 per group
- Key decision-making endpoints is a continuous landmark endpoint
- Objectives:
  - Estimate E-R relationship in Phase 2 population
  - Predict E-R in Phase 3 population and impact on dose selection
Observed data show an apparent E-R relationship...
Observed data show an apparent E-R relationship . . .

There also appears to be an association with a covariate, $x_1$. 
Example of exposure-response with multiple doses

... and two covariates are associated with exposure
Exposure-response models

4-parameter Emax model for efficacy:

\[ Y_i = \theta_0 + \frac{\text{Emax}_i \cdot C_{avg}^{\gamma}}{\text{EC50}^{\gamma} + C_{avg}^{\gamma}} + \epsilon_i \]

\[ \epsilon_i \sim N(0, \sigma^2) \]

We will model the maximum effect as a function of \( X1 \):

\[ \text{Emax}_i = \theta_1 + \theta_2 \cdot x_{1i} \]

\[ \text{EC50} = \exp(\theta_3) \]

\[ \gamma = \exp(\theta_4) \]
Example of exposure-response with multiple doses

Fitted model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\theta_0$</td>
<td>9.56</td>
<td>(8.79, 10.3)</td>
</tr>
<tr>
<td>$\theta_1$</td>
<td>9.91</td>
<td>(8.18, 18.1)</td>
</tr>
<tr>
<td>$\theta_2$</td>
<td>1.43</td>
<td>(0.60, 2.99)</td>
</tr>
<tr>
<td>EC50</td>
<td>29.7</td>
<td>(20.0, 44.0)</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>1.63</td>
<td>(0.74, 3.60)</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>1.92</td>
<td></td>
</tr>
</tbody>
</table>
Extrapolation to phase 3 population

Based on the planned inclusion criteria the Phase 3 population is expected to have different distributions for $X_1$ and $X_2$. 

![Graph showing distributions for Phase 2 and Phase 3 populations for $X_1$ and $X_2$.]
Higher response given exposure

Lower exposure given covariates
How do we translate this to dose-response?

If we focus on the expected response, then

\[ E(Y \mid \text{dose}, X) = \int E(Y \mid C_{avgs}, X) f(C_{avgs} \mid \text{dose}, X) dC_{avgs} \]

and

\[ E(Y \mid \text{dose}, \text{Popn}) = \int E(Y \mid C_{avgs}, X) f(C_{avgs} \mid \text{dose}, X) f(X \mid \text{Popn}) dC_{avgs} \ dX \]
A 4 mg dose gives \( \sim \) 85\% of maximal response in Phase 2 population.

Equivalent expected response at 6 mg dose in Phase 3 population.

Potential for higher response rates in Phase 3 population at higher doses?
<table>
<thead>
<tr>
<th>Dose</th>
<th>Exposure</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Example of exposure-response with multiple doses

Covariates
Can we use E-R modeling when we’ve only studied one dose?

- Sometimes (e.g. in oncology), a single dose is studied in Phase 2 (and Phase 3).
- We may have some variation in exposure . . .
- . . . but what if exposure is related to measured (or unmeasured) confounding variables?
An apparent exposure-response relationship...

Suppose we want to...

- Estimate exposure-response relationship on the hazard ratio for trastuzumab relative to control.
- Estimate the hazard ratio for Q1 relative to control.
- Predict the effects of a higher dose in patients with lower exposure.

...in an unbiased (causal) manner.

What if there are covariates associated with exposure and outcome . . .

Table 2. Summary of categorical covariates in low-exposure vs high-exposure patients in the T+FC arm.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>First Quartile (n = 67), %</th>
<th>Combined Second to Fourth Quartiles (n = 199), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>14.9</td>
<td>40.2</td>
</tr>
<tr>
<td>1</td>
<td>61.2</td>
<td>454.8</td>
</tr>
<tr>
<td>2</td>
<td>23.9</td>
<td>5.0</td>
</tr>
<tr>
<td>Prior gastrectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13.6</td>
<td>29.7</td>
</tr>
<tr>
<td>No</td>
<td>86.4</td>
<td>70.3</td>
</tr>
<tr>
<td>Number of metastatic sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2</td>
<td>64.2</td>
<td>40.4</td>
</tr>
<tr>
<td>1-2</td>
<td>35.8</td>
<td>59.6</td>
</tr>
<tr>
<td>Asian ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>46.3</td>
<td>57.3</td>
</tr>
<tr>
<td>No</td>
<td>53.7</td>
<td>42.7</td>
</tr>
<tr>
<td>IHC3+ status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>47.8</td>
<td>48.7</td>
</tr>
<tr>
<td>No</td>
<td>52.2</td>
<td>51.3</td>
</tr>
</tbody>
</table>

A stepwise Cox regression model identified 5 negative prognostic factors for OS: ECOG PS; no prior gastrectomy; non-Asian; immunohistochemistry (IHC) 0, 1, or 2+ HER2 tumor overexpression; and more than 2 sites of metastatic disease. The exposure of trastuzumab remained a significant ($P < .05$) contribution to the OS after adjusting for these risk factors. In addition to the 5 listed variables, we also tested other variables such as age (continuous), age ($\geq 60$ vs $< 60$ years), body weight, body surface area, extent of disease (local vs metastatic), gender, primary site (stomach vs gastroesophageal junction), and type of cancer (mixed vs intestinal, diffuse vs intestinal). These are not significant contributors for overall survival in the phase 3 trial.

Yang et al. (2012) The Combination of Exposure-Response and Case-Control Analyses in Regulatory Decision Making
Exposure-response with one dose?

... and the distribution is different across the exposure range?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Before Matching</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FC</td>
<td>Q1 T+FC</td>
</tr>
<tr>
<td>No.</td>
<td>296</td>
<td></td>
</tr>
<tr>
<td>ECOG PS (0-1 vs 2)</td>
<td>0.909</td>
<td>0.761</td>
</tr>
<tr>
<td>Prior surgery (yes vs no)</td>
<td>0.213</td>
<td>0.134</td>
</tr>
<tr>
<td>Asia (yes vs no)</td>
<td>0.561</td>
<td>0.463</td>
</tr>
<tr>
<td>Number of metastatic sites (1-2 vs &gt;2)</td>
<td>0.505</td>
<td>0.358</td>
</tr>
<tr>
<td>IHC3+ status (yes vs no)</td>
<td>0.483</td>
<td>0.478</td>
</tr>
</tbody>
</table>

Yang et al. (2012) The Combination of Exposure-Response and Case-Control Analyses in Regulatory Decision Making
Potential solutions to confounded E-R

- Include potential confounders as covariates in the E-R model
- Treat the analysis as if it were from an observational study (e.g., using matching)
  - Categorize exposure (e.g., quantiles)
  - Calculate propensity scores (for each exposure category relative to placebo)
  - Use for matched or weighted regression analyses
Exposure-response modeling is a key ingredient in drug development

- Uses an understanding of pharmacology of the drug (dose $\rightarrow$ exposure)
- May allow the use of models closely tied to the action of the drug (exposure $\rightarrow$ response)
- Need to consider potential for confounding/effect modification (particularly if E-R based on one dose level)
Many opportunities for interdisciplinary collaboration

- Identifying development questions to address through exposure-response modeling (at portfolio level as well as compound level)
- Design of studies to inform exposure-response modeling
- Execution of M&S work

What can statisticians do to get more involved?

- Be open to learning a new topic
- Share what you do know in a collaborative manner (e.g., knowledge of study population vs. knowledge of pharmacology)
Back-up Slides
E-R for what endpoints? (editorial aside)

- E-R is most believable when you’re modeling endpoints that are most closely related to the mechanism of action of the drug.
  - Concentration of drug $\rightarrow$ biomarker (possibly with a delayed effect)

- As we move farther away from MOA, K-PD or summary measures of exposure may be reasonable
  - e.g., average concentration $\rightarrow$ tumor growth inhibition

- Even farther away, we may need to rely on some scientifically-based hand waving
  - e.g., Average concentration in Cycle 1 $\rightarrow$ survival