Escalation Strategies for Combination Therapy Phase I Trials

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Outline

- Phase I trials
- Dual-agent (combination therapy) trials
- Parametric models for dose-toxicity relationship
- Escalation strategies
  - Admissible doses
  - Decision rules
- Simulation study
- Conclusions
Phase I trials

Aim

- First experimentation of a new drug / clinical procedure in human subjects
- Find a safe, yet potentially effective, dose for future Phase II experimentation
- Seek the highest possible dose subject to toxicity constraints, known as the *maximum tolerated dose* (MTD)

Dose-escalation

- Ethical considerations require low starting dose
- Patients enrolled in a sequential fashion at different dose levels
- Bayesian adaptive designs (*e.g.* the CRM (O’Quigley, 1990)) used to choose the next dose
Phase I trials

Combination therapies

- Becoming increasingly common in the treatment of many diseases (e.g. cancer, HIV)
- Many designs are still quite naive
  - e.g. fix dose of one agent, and dose-escalate the other (using single-agent designs)
- Unknown synergistic/antagonistic effects
- Require simultaneous dose-escalation
- Aims and objectives must differ from single-agent trials
  - Multiple MTDs may exist
  - More prior information (from single-agent trials)
  - Multiple outcomes (toxicity and efficacy)
Let $\mathbf{x} = (x_{Ai}, x_{Bj})$ be the dose combination when drug A is used at level $i$ ($i = 1, \ldots, I$) and drug B is used as level $j$, ($j = 1, \ldots, J$).

Assume a parametric model $\pi(\mathbf{x}, \theta)$, for example...

**Thall et al., Biometrics, 2003.**

\[
\pi(\mathbf{x}; \theta_1) = \frac{\alpha_1 x_{Ai}^{\beta_1} + \alpha_2 x_{Bj}^{\beta_2} + \alpha_3 (x_{Ai}^{\beta_1} x_{Bj}^{\beta_2})^{\beta_3}}{1 + \alpha_1 x_{Ai}^{\beta_1} + \alpha_2 x_{Bj}^{\beta_2} + \alpha_3 (x_{Ai}^{\beta_1} x_{Bj}^{\beta_2})^{\beta_3}}
\]

**Yin and Yuan, JRSS Series C, 2009.**

\[
\pi(\mathbf{x}; \theta_2) = 1 - \left\{ \left(1 - f(x_{Ai})^{\delta}\right)^{-\gamma} + (1 - g(x_{Bj})^{\psi})^{-\gamma} - 1 \right\}^{-1/\gamma}
\]
Contours of toxicity

For specified model parameters, can obtain various dose-toxicity surfaces.

Synergy
Antagonism

Drug A
Drug B
Probability DLT
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
Escalation and updating

- Specify an initial dose-combination for first cohort, $x_1 = (x_A, x_B)$
- Count the number of toxicities to occur
- Given a parametric dose-toxicity model, $\pi(x; \theta)$, with priors
  - Update inferences to obtain new posterior distribution
- Choose next dose combination based on
  1. A set of admissible dose combinations
  2. A decision rule to choose between admissible doses, using the posterior distribution
- Continue recruiting patients until either
  - a fixed sample size is obtained
  - the precision of a certain quantity reaches a pre-specified level
Admissible dose combinations

- For a discrete set of dose levels, constraints are placed on escalation
- Strategy $\Omega_{\text{ndiag}}$: Non-diagonal escalation
- Strategy $\Omega_{\text{diag}}$: Diagonal escalation
Strategy $\Omega_{prev}$: Diagonal escalation + any previously experimented dose combination
Decision rules

**Strategy $D_{pat}$: Patient gain**

- Amongst admissible doses, choose the one whose posterior mean probability of toxicity is closest to the TTL, $\nu$

\[ x_{n+1} = \arg \min_{\xi \in \Omega} |E[\pi(\xi; \theta) | Z_n] - \nu| \]

**Strategy $D_{var}$: Variance gain**

- Amongst admissible doses, choose the one that will allow us to gain most information about the parameters
- Constrained Bayesian D-optimality design

\[ x_{n+1} = \arg \max_{\xi \in \Omega} E \left[ \log \det \left( \sum_{i=1}^{n} l(x_i; \theta) + l(\xi; \theta) \right) \right] | Z_n \]

where $l(x; \theta)$ is the Fisher information matrix associated with treating a patient at dose combination $x$
Decision rules

**Strategy $D_{\text{var}}$: Variance / patient gain**

- The pure variance gain strategy, $D^*_{\text{var}}$, could be unsafe
- Need to account for patient gain
- A solution: Further restrict admissible dose set
  $$\Omega_{\varepsilon} = \Omega \cap \{\xi; |E[\pi(\xi; \theta) | Z_n] - v| \leq \varepsilon\}$$
  
- "Pure" patient gain: $\varepsilon \to 0$
- "Pure" variance gain: $\varepsilon \to \infty$
Simulation study

Priors (for six-parameter model)

Scenarios

True probabilities of toxicity...

1. ... in agreement with prior mean
2. ... higher than prior mean
3. ... are asymmetric
4. ... are flat
Simulation study

Simulation set-up

- Six dose levels per drug
- \( TTL = 0.30 \), with \( \varepsilon = 0.025 \) for \( D_{var} \) designs
- Sample size = 40 (with 2 patients per cohort)
- Prior as in Scenario 1
- 1000 simulations performed for each scenario and design/admissible dose combination \((D_{pat}, D_{var}) \times (\Omega_{ndiag}, \Omega_{diag}, \Omega_{prev})\)

Recommended Phase II doses

1. Must have been experimented on during trial
2. Posterior mean \( p(DLT) \) within \( \varepsilon \) of the TTL
Dose-escalation by admissible dose set

![Graph showing dose-escalation](image-url)
Experimentation: Scenario 1

Non-Diagonal escalation proceeds along the margins.
Experimentation: Scenario 1

More varied experimentation using D-optimal designs

Non-Diagonal escalation proceeds along the margins
## Recommended dose combinations

<table>
<thead>
<tr>
<th>Decision rule Admissible set</th>
<th>$D_{\text{pat}}$</th>
<th>$D_{\text{var}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\Omega_{\text{ndiag}}$</td>
<td>$\Omega_{\text{diag}}$</td>
</tr>
<tr>
<td><strong>Scenario 1 - In agreement with prior</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity (%)</td>
<td>$0 - 14$</td>
<td>$1.4$</td>
</tr>
<tr>
<td></td>
<td>$15 - 24$</td>
<td>$19.6$</td>
</tr>
<tr>
<td></td>
<td>$25 - 34$</td>
<td>$58.4$</td>
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<tr>
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<td>$35 - 44$</td>
<td>$20.7$</td>
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<td></td>
<td>$\geq 45$</td>
<td>$0.0$</td>
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<tr>
<td>% of MTDs selected</td>
<td>$16$</td>
<td>$18$</td>
</tr>
<tr>
<td><strong>Scenario 2 - Toxic</strong></td>
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<td></td>
</tr>
<tr>
<td>Toxicity (%)</td>
<td>$0 - 14$</td>
<td>$1.0$</td>
</tr>
<tr>
<td></td>
<td>$15 - 24$</td>
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<td>$25 - 34$</td>
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<td>$35 - 44$</td>
<td>$23.5$</td>
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<td></td>
<td>$\geq 45$</td>
<td>$3.3$</td>
</tr>
<tr>
<td>% of MTDs selected</td>
<td>$18$</td>
<td>$21$</td>
</tr>
</tbody>
</table>
Summary

- Escalation strategies more complex for combination therapies

- Non-diagonal escalation rarely behaves in a step-like manner
  - May get ‘stuck’ in regions where one drug is given at a low dose

- Less constrained algorithms...
  - ... allow more flexible experimentation
  - ... place more faith on the underlying model

- D-optimal designs allow for varied experimentation
  - This allows more drug combinations to be recommended
  - Trade-off between ‘patient’ and ‘variance’ gain decisions
  - Other optimal designs (C-opt, Dc-opt) require investigation and may enhance operating characteristics

- Methodology could be extended to incorporate other outcomes
  - Emerging PK/PD information collected at the doses
  - Efficacy biomarkers / clinical response
  - Decision rules could *penalise* non-effective doses from being chosen
