Designs for Phase I Trials of Combinations of Agents

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Outline

• Brief description of single agent phase I trials
• Examples of combination-agent trials
  – Enumerate all orderings
  – Many orderings
• Problems with small sample size and large number of possible “treatments” (combinations of agents)
Single Agent Phase I Trials

• Typical statistical set-up:
  – Preset dose levels $d_1 < d_2 < \ldots < d_K$
  – Binary measure of toxicity

  \[ \pi_j = \text{Prob patient receiving dose level } j \text{ experiences a "dose-limiting toxicity" (DLT)} \]

• Primary goal: Find maximum tolerated dose (MTD)
Single Agent Phase I trials

- MTD: highest dose that can be administered with an “acceptable” level of toxicity
  - “acceptable”: Probability of toxicity is no more than a pre-specified amount
    - Often 20% or 33%
- Ethical considerations dictate that trials are done sequentially
  - Patients not allocated to dose level \(d_j\) unless levels \(d_1, \ldots, d_{j-1}\) are believed to be “safe”
Many designs proposed in this setting

- Traditional (or “standard” or “3 + 3”)
- Storer 2-stage
- Up-and-down
- *Continual Reassessment Method (CRM)*
- Recently proposed Bayesian methods
CRM set-up

• Fixed number of dose levels: $d_1, d_2, \ldots, d_K$

• Use a “working model” for the probability of toxicity at dose level $j$:

$$\pi_j = (\psi_j)^a, \text{ where } 0 < \psi_1 < \psi_2 < \ldots \psi_K < 1$$

Ψ’s are pre-set

‘a’ is a parameter to be estimated
Two-stage, likelihood version
O’Quigley and Shen, Biocs 1996

• Stage I. Use any ‘non-model’ type design (any of Storer’s stage 1, or up-and-down or..)
  – E.g. Start at dose level 1
  – Escalate in single patient cohorts
  – Once a toxicity is observed, start stage II

• Stage II: Have toxicity and number of patients \{Y_j, N_j\} on dose levels 1, \ldots, K
  – Likelihood:
    \[
    \prod_{j=1}^{K} \left( \frac{\alpha^{n_j}}{\alpha^{n_j} + \beta^{n_j-y_j}} \right)
    \]
Estimate ‘a’

• Estimate a by maximum likelihood ($\hat{a}$)
• Plug back into working model
  $\psi_1 \hat{a}, \psi_2 \hat{a}, \ldots, \psi_K \hat{a}$

• Next patient goes on dose level closest to target toxicity probability that defines the MTD
2-stage CRM

- Continue ‘estimate/allocate’ cycle until a fixed number of patients have been observed

- MTD estimate is recommended dose level for the next patient

- CRM has excellent statistical properties in terms of identifying the MTD
### Partially-ordered trials

Toxicity probabilities follow a “partial order”: there exist pairs of combinations for which the ordering of toxicity probabilities is not known.

<table>
<thead>
<tr>
<th>Combination</th>
<th>Pacitaxel</th>
<th>Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>67.5</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>81</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>94.5</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>67.5</td>
<td>7.5</td>
</tr>
<tr>
<td>6</td>
<td>67.5</td>
<td>9</td>
</tr>
</tbody>
</table>

Patnaik et al. (2000, Journal of Clin Onc)
Compare to single agent trials

• Same:
  – Need to do the dose allocation sequentially

• Different
  – Toxicity probabilities follow a partial order
Wages, Conaway and O’Quigley (2011, Clinical Trials)

• Stage 1. Single patient escalation through “zones”

• After a toxicity is observed, start stage II.
CRM for Partial Orders

• Consider each (complete) order that is consistent with the partial order.

• Intuition: If we knew which one was the “correct” order, we could just use usual CRM

<table>
<thead>
<tr>
<th>Comp Order</th>
<th>Ordering</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>1 – 2 – 3 – 4 – 5 – 6</td>
</tr>
<tr>
<td>M2</td>
<td>1 – 2 – 3 – 5 – 4 – 6</td>
</tr>
<tr>
<td>M3</td>
<td>1 – 2 – 3 – 5 – 6 – 4</td>
</tr>
<tr>
<td>M4</td>
<td>1 – 2 – 5 – 3 – 4 – 6</td>
</tr>
<tr>
<td>M5</td>
<td>1 – 2 – 5 – 3 – 6 – 4</td>
</tr>
<tr>
<td>M6</td>
<td>1 – 2 – 5 – 6 – 3 – 4</td>
</tr>
</tbody>
</table>
CRM for partial orders

• ‘Two-parameter’ version of CRM
  – One parameter indexes the ordering
  – Within a given ordering, usual CRM set-up

• The working model for the probability of toxicity for combination i in ordering M=m is

\[ \Psi_{im}^{am} \]
## Example of working model

<table>
<thead>
<tr>
<th>M</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (1-2-3-4-5-6)</td>
<td>(.01)^a1</td>
<td>(.05)^a1</td>
<td>(.10)^a1</td>
<td>(.20)^a1</td>
<td>(.33)^a1</td>
<td>(.50)^a1</td>
</tr>
<tr>
<td>2 (1-2-3-5-4-6)</td>
<td>(.01)^a2</td>
<td>(.05)^a2</td>
<td>(.10)^a2</td>
<td>(.33)^a2</td>
<td>(.20)^a2</td>
<td>(.50)^a2</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>6 (1-2-5-6-3-4)</td>
<td>(.01)^a6</td>
<td>(.05)^a6</td>
<td>(.33)^a6</td>
<td>(.50)^a6</td>
<td>(.10)^a6</td>
<td>(.20)^a6</td>
</tr>
</tbody>
</table>

Working model consistent with the ordering.
Allocation method

• As data accumulates, estimate ‘$a_m$’ for each ordering by maximum likelihood
  • Choose ordering with largest likelihood

• Update estimate of toxicity probabilities for dose combinations within that ordering

• Next patient goes on dose combination with the estimated toxicity probability closest to the target
How well does it work?

• Wages, Conaway and O’Quigley (2011) present results of simulations assessing how well this identifies the MTD

• Comparisons to other methods for partially ordered trials:
  – Similar to Conaway, Dunbar and Peddada (2004) in identifying MTD
  – Not as often as CRM when you know the ordering
## Illustration

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>①</td>
<td>0.05</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.002</td>
<td>0</td>
</tr>
<tr>
<td>②</td>
<td>0.10</td>
<td>0.004</td>
<td>0.006</td>
<td>0.026</td>
<td>0.022</td>
<td>0.010</td>
</tr>
<tr>
<td>③</td>
<td>0.20</td>
<td>0.196</td>
<td>0.185</td>
<td>0.486</td>
<td>0.339</td>
<td>0.247</td>
</tr>
<tr>
<td>⑤</td>
<td>0.33</td>
<td>0.571</td>
<td>0.529</td>
<td>0.237</td>
<td>0.438</td>
<td>0.412</td>
</tr>
<tr>
<td>④</td>
<td>0.45</td>
<td>0.220</td>
<td>0.269</td>
<td>0.024</td>
<td>0.143</td>
<td>0.264</td>
</tr>
<tr>
<td>⑥</td>
<td>0.60</td>
<td>0.010</td>
<td>0.011</td>
<td>0.227</td>
<td>0.056</td>
<td>0.067</td>
</tr>
</tbody>
</table>

Summary: \( \sum (% \text{ recommended}) | \pi_i - \text{target} | \)
Without over-interpreting one set of true probabilities....

• If the ordering is known, problem reduces to single agent (usual) case
  – O’Quigley & Shen design gives results similar to optimal benchmark

• If guess incorrectly at the ordering and use a method relying on that ordering, poor properties in terms of estimating MTD
For one set of true probabilities...

• WCO and CDP have similar properties
  – Other cases, one may do better than the other, but in general similar properties
  – WCO computationally simpler

• Identifies MTD less often than when true ordering is known
  – In other cases, performance can be similar to case where true ordering is known
Could we weight the orderings?

- Wages, Conaway and O’Quigley (2011, Biometrics)
  - Uses model from first patient on
    - Not a 2-stage
    - Bayesian method
  - Allows prior weighting of orderings
  - Still considers all possible orderings consistent with partial order
## Combination agent trials

<table>
<thead>
<tr>
<th>Dose of agent 1</th>
<th>Dose of agent 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>25</td>
<td>①</td>
</tr>
<tr>
<td>100</td>
<td>④</td>
</tr>
<tr>
<td>400</td>
<td>⑦</td>
</tr>
<tr>
<td>1600</td>
<td>⑩</td>
</tr>
</tbody>
</table>
Methods

- Thall, Millikan, Mueller, Lee (2003, Biometrics)
- Conaway, Dunbar and Peddada (2004, Biometrics)
- Wang and Ivanova (2005, Biometrics)
- Yin and Yuan
  - 2008, Stat in Med
  - 2009 Applied Stat
  - 2009 Biometrics
- Braun and Wang (2010, Biometrics)
- Thall, Nguyen, Paoletti, Kramar (2010, Biometrics)
- Braun and Alonzo (2011, Clinical Trials)
- Wages, Conaway and O’Quigley
  - Biometrics, 2011
  - Clinical Trials, 2011
  - Under review, 2012
What makes this different?

- Stage I not different
  - Escalate through zones
  - Toxicity known to increase across zones, unknown within

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>Zone 1</td>
<td>Zone 2</td>
<td>Zone 3</td>
</tr>
<tr>
<td>100</td>
<td>Zone 2</td>
<td>Zone 3</td>
<td>Zone 4</td>
</tr>
<tr>
<td>400</td>
<td>Zone 3</td>
<td>Zone 4</td>
<td>Zone 5</td>
</tr>
<tr>
<td>1600</td>
<td>Zone 4</td>
<td>Zone 5</td>
<td>Zone 6</td>
</tr>
</tbody>
</table>
Why is this different? Stage II

• Is it reasonable to consider all the possible orderings?

• If choose subset:
  – Is it important to have the correct order as one of the subset?
    • If yes, would that imply the subset should be large?
    • If no, would that imply the subset could be small?
      – Note: In the previous, the “correct” order was always in the set because we considered all of them
How to choose orderings?

• Type/dose of agents may give a ‘natural’ ordering
• Previous uses of these agents
• Spread them out over the design space
  – (J. Huesing)
• Choose ‘generic’ orders
  – Conjecture: these are sufficiently spread across the design space
Recommended set of orders

• Across columns
  1-2-3-4-5-6-7-8-9-10-11-12

• Down Rows:
  1-4-7-10-2-5-8-11-3-6-9-12

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>11</td>
<td>12</td>
</tr>
</tbody>
</table>
Recommended set of orders

• Diagonal ‘1’
  1-2-4-3-5-7-6-8-10-9-11-12

• Diagonal ‘1’ reversed within zones
  1-4-2-7-5-3-10-8-6-11-9-12
A couple more possibilities

• ‘Switchback 1’
  1-2-4-7-5-3-6-8-10-11-9-12

• ‘Switchback 2’
  1-4-2-3-5-7-10-8-6-9-11-12
What effect does the choice have?

• Wages, O’Quigley and Conaway (submitted) investigate a 4 x 4 case

• Consider the use of 3, 6, or 9 orders

• Answer is complicated: depends on where MTD is in the table
In general

- 6 chosen orders
  - provides a good compromise even when ‘true’ ordering is not one of the set.
  - At times, can perform nearly as well as knowing the ordering.
Summary

• Generalization of CRM to partial orders
  – Good properties when it is possible to enumerate all orderings

• When it is not possible to enumerate orderings
  – Can incorporate prior knowledge of orderings
  – Has good properties when ‘general’ choice of orderings is used.