The Continual Reassessment Method: New directions and old roadblocks

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The Continual Reassessment Method (CRM)

- Originally devised by O’Quigley, Pepe and Fisher (1990) where dose for next patient was determined based on responses of patients previously treated in the trial.

- Based on dose-finding for MTD – assumes goal is to find dose-toxicity relationship.

- Due to safety concerns, several authors developed variants rather quickly:
  - Modified CRM (Goodman et al. 1995)
  - Extended CRM [2 stage] (Moller, 1995)
  - Restricted CRM (Moller, 1995)
  - and others....
Attributes of the CRM

• Mathematical dose-toxicity model must be assumed
• We choose the level of toxicity that we desire for the MTD (e.g., $p = 0.20$)
• At end of trial, we can estimate dose response curve.
• Prior distribution needs to be specified
• Other methods
  – EWOC (Escalation with Overdose Control (Babb et al. 1998))
  – Bayesian adaptive
  – likelihood-based versions of CRM (Piantadosi et al. 1998)
Example
Easy Software

- Practical CRM (Piantadosi et al. 1998)
- EWOC (Babb et al. 1998)
New directions

- Old paradigm: cytotoxic agents
- New paradigm: biologically optimal dose (BOD)
  - low toxicity,
  - biomarkers to assess “mechanism”
  - still need to include toxicity
- Toxicity and efficacy combination define BOD
- TriCRM (Zhang et al. 2007)
  - three category outcome
    - no efficacy, no toxicity
    - efficacy, no toxicity
    - toxicity
  - continuation ratio model
  - Statistically very appealing
  - Why not widely accepted???
Multiple Agents

- **Thall et al. (2003):** Proposed a two-stage Bayesian design for identifying one or more acceptable dose pairs including characterizing agent-agent interactions
- **Conaway et al. (2004):** Proposed a quasi-Bayesian design based on partial ordering of the toxicity probabilities (i.e., when the monotonicity of the dose-toxicity curve is not completely known at the start of the trial)
- **Wang and Ivanova (2005):** Proposed a Bayesian design to identify the MTD of one agent in combination with each of the possible doses of the second agent
- **Mandrekar, Cui, Sargent (2007):** Extended the TriCRM to handle multiple agents

- *Widely accepted? Again, NO!*
CRM vs. Not

• CRM appropriate
  – optimal dose is the goal
  – dose-response or dose-toxicity relationship not of interest

• Dose-ranging appropriate
  – interest in response over a range
  – other outcomes of interest over range
    • pharmacokinetics
    • pharmacodynamics
So, are these methods working?

• NO!

• Some scientific reasons:
  – lack of biomarkers of efficacy
  – poor performance of assays
  – lack of ability to perform in real-time
  – dissatisfaction with dichotomous efficacy

• But, for cytotoxic agents? why not?
How far has the CRM come?

- Rogatko et al., 2007
- Literature review of phase I cancer studies and phase I design papers, 1991-2006
- 1,235 clinical studies and 90 design papers
- Results:
  - 1.6% of trials followed novel design (n=20)
    - 1.4% were CRM (n=17)
  - 98.4% of trials used variations of up-down designs
- Reasons cannot be just scientific!
Practical Roadblocks

- lack of familiarity
- “black box”
- lack of control/reliance on statisticians
- fear of regulatory acceptance
  - IRBs
  - FDA
  - CTEP
- regulatory rejection
- disinterest is trail-blazing
- time commitment/consumption
Steps towards acceptance

- Regulatory agency encouragement of novel designs
  - NIH/NCI reviewers need to ask for novel designs
  - FDA needs to condone novel designs

- Statisticians need to:
  - promote existing methods more strongly: provide incentives to statisticians!
  - stop developing new ones: the novel designs have proven to be similarly appropriate for dose identification (Zohar and Chevret, 2008)

- Translation from statistical literature to medical literature
  - education of regulators
  - education of clinicians
Credits and References (1)

Thanks to Dan Sargent (Mayo Clinic)

References


• Moller S. An extension of the continual reassessment methods using a preliminary up-and-down design in a dose finding study in cancer patients, in order to investigate a greater range of doses. Stat Med. 1995 May 15-30;14(9-10):911-22; discussion 923.
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