A Simple Approach For Incorporating Multiple Toxicity Thresholds In Phase I Trials

Jieling Miao and Shing M. Lee

Columbia University, Department of Biostatistics

May 20, 2015
Phase I trials

Phase I clinical trials
- Typically small studies
- Evaluate safety and identify a dose for further study

Toxicity
- Grades (from 0 to 5) for severity of adverse events (AE) provided by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

Dose-limiting Toxicity (DLT)
- Usually summarize toxicity into a binary DLT outcome
- In most phase I cancer clinical trials, a DLT is defined as a grade 3 or higher toxicity according to the NCI CTCAE

Maximum Tolerated Dose (MTD)
- The dose associated with a pre-specified probability ($\theta$) of DLT
- MTD is defined as the dose level whose toxicity probability is closest to $\theta$. 
Multiple toxicity gradations

- DLT does not take into account toxicity gradations
- However, sometimes interested in various gradations of toxicity
- Consider an example:
  Phase I trial in lymphoma patients treated with bortezomib plus the standard CHOP-Rituximab regimen.
  Grade 3 neuropathy is symptomatic toxicity interfering with activities of daily life, resolved by treatment VS.
  Grade 4 neuropathy is life threatening or disabling and hence irreversible.
- Wish to specify different thresholds
  - $\theta_3$ is the target toxicity probability for $Y \geq 3$
  - $\theta_4$ is the target toxicity probability for $Y \geq 4$
Continual Reassessment Method (CRM) for binary outcome

- Model-based method for dose finding
- Start with an assumed dose toxicity curve and a chosen target toxicity rate
- After observing a patient’s toxicity outcome, dose toxicity curve re-fit and model parameter(s) re-estimated, using Bayesian or maximum likelihood methods
- Next person assigned dose with estimated toxicity probability closest to the target rate
- Repeat until a specific sample size is met
Design parameters to be specified for CRM

- target DLT probability $\theta$ for $Y \geq 3$
- number of doses/dose levels
- prior MTD
- sample size
- dose toxicity model $F(\cdot, \beta)$
- prior distribution for model parameters $\beta$
- skeleton - initial guess of toxicity probabilities for each dose, which provides rescaled dose levels by backward substitution
Existing methods

- Method 1: Bayesian CRM with multiple toxicity constraints
  Lee SM, Cheng B, Cheung YK Biostatistics 2010 paper

- Method 2: Likelihood CRM with multiple toxicity constraints
  Cheng B, Lee SM Journal of Statistical Planning and Inference 2015 paper

- Other methods:
  Model as an Ordinal Outcome (0-5) using, for example, a
  Proportional Odds Model
  2 stage design with lower grades
Proposed methods

Approach

- Two chosen target toxicity rates \((\theta_3, \theta_4)\)
- After getting the toxicity data, create two binary outcomes based on the two thresholds \((Y \geq 3, Y \geq 4)\).
- Use two CRMs independently to find the recommended dose levels based on each threshold. That is

\[
x_3 = \arg \min_x |F_3(x, \hat{\beta}_3) - \theta_3|
\]

\[
x_4 = \arg \min_x |F_4(x, \hat{\beta}_4) - \theta_4|
\]

where \(x\) is the dose level and \(F_3(\cdot, \hat{\beta}_3)\) and \(F_4(\cdot, \hat{\beta}_4)\) are models for the two toxicity outcomes

- MIN: assign dose of \(\min\{x_3, x_4\}\) to the next patients
Design parameters for simulation study

- Applied to the bortezomib lymphoma trial
- Target toxicity probability $\theta_3 = 0.25$, $\theta_4 = 0.10$
- Dose levels $K = 5$
- Prior MTD = 3
- Sample size = 18
- Dose toxicity models: $F_3(d, \beta_3) = d^{\exp(\beta_3)}$, $F_4(d, \beta_4) = d^{\exp(\beta_4)}$
- Skeleton: optimal pair $(\delta_3, \delta_4) = (0.08, 0.05)$, using similar approach by Lee and Cheung (2009) to get the optimal $\delta$.

Grid search for optimal $(\delta_3, \delta_4)$ pair
Comparison of proposed method (MIN) to CRM, MCB, MCL

MTD3 and MTD4 match at dose 3

MTD3 and MTD4 match at dose 5
Comparison of proposed method (MIN) to CRM, MCB, MCL

MTD3 at dose 3; MTD4 at dose 4

MTD3 at dose 3; MTD4 at dose 2
Conclusions

- When $\text{MTD3} > \text{MTD4}$, CRM fails to choose the right dose, since it does not take into account the secondary constraint.
- $\text{MIN}$, $\text{MCB}$, and $\text{MCL}$ perform equally well except when the target dose is the highest level.
- $\text{MIN}$ is simple and can be easily implemented, using existing dfcrm R package.
References

Acknowledgments

- Shing M Lee
- Jimmy K Duong
- Bin Cheng
- Ken YK Cheung
- Dose finding working group at Columbia University, Department of Biostatistics