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

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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 (θ) of DLT
- MTD is defined as the dose level whose toxicity probability is closest to θ.

Multiple toxicity gradations

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
  θ_3 is the target toxicity probability for $Y \geq 3$
  θ_4 is the target toxicity probability for $Y \geq 4$

CRM

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

CRM

Design parameters to be specified for CRM

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

Existing methods

- Method1: Bayesian CRM with multiple toxicity constraints
  Lee SM, Cheng B, Cheung YK Biostatistics 2010 paper
- Method2: 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 (θ_3, θ_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

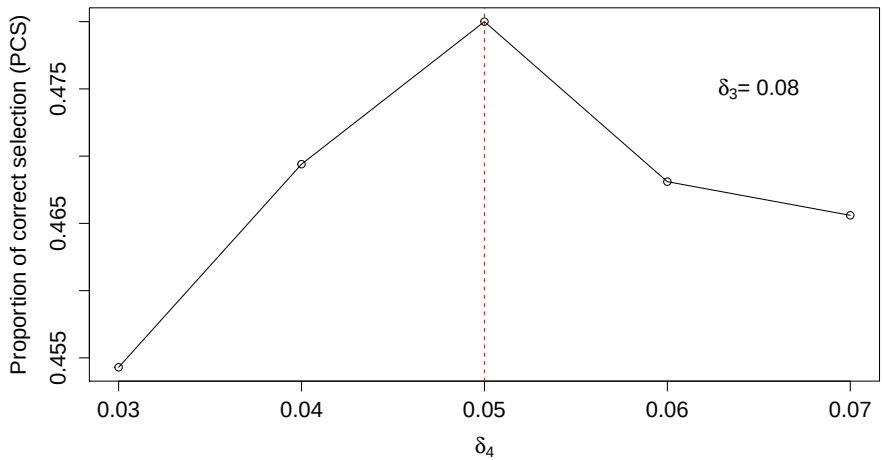
$$x_3 = \arg\min_x |F_3(x, \hat{\beta}_3) - \theta_3|$$
$$x_4 = \arg\min_x |F_4(x, \hat{\beta}_4) - \theta_4|$$

  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

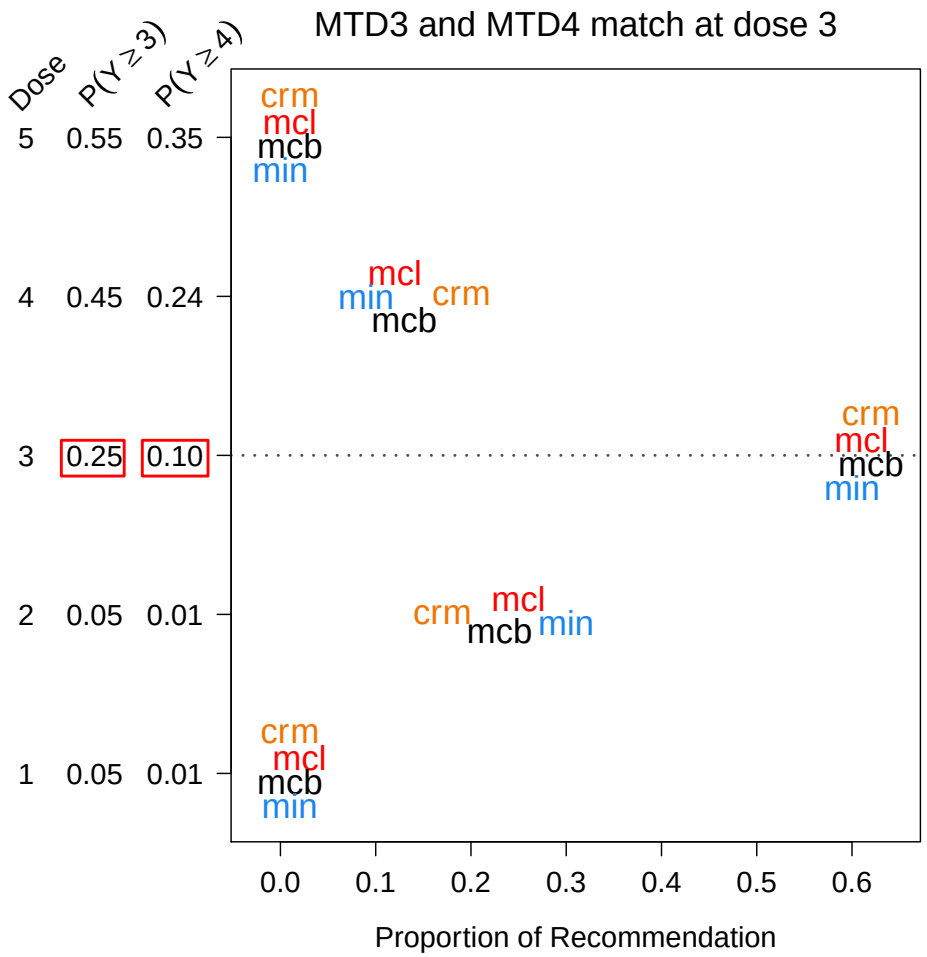
- Applied to the bortezomib lymphoma trial
- Target toxicity probability $\theta_3 = 0.25, \theta_4 = 0.10$
- Dose levels $K = 5$
- Prior MTD $= 3$
- Sample size $= 18$
- Dose toxicity models: $F_3(d, \beta_3) = d^{\exp(\beta_3)}$, $F_4(d, \beta_4) = d^{\exp(\beta_4)}$
- Skeleton: optimal pair $(\delta_3,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

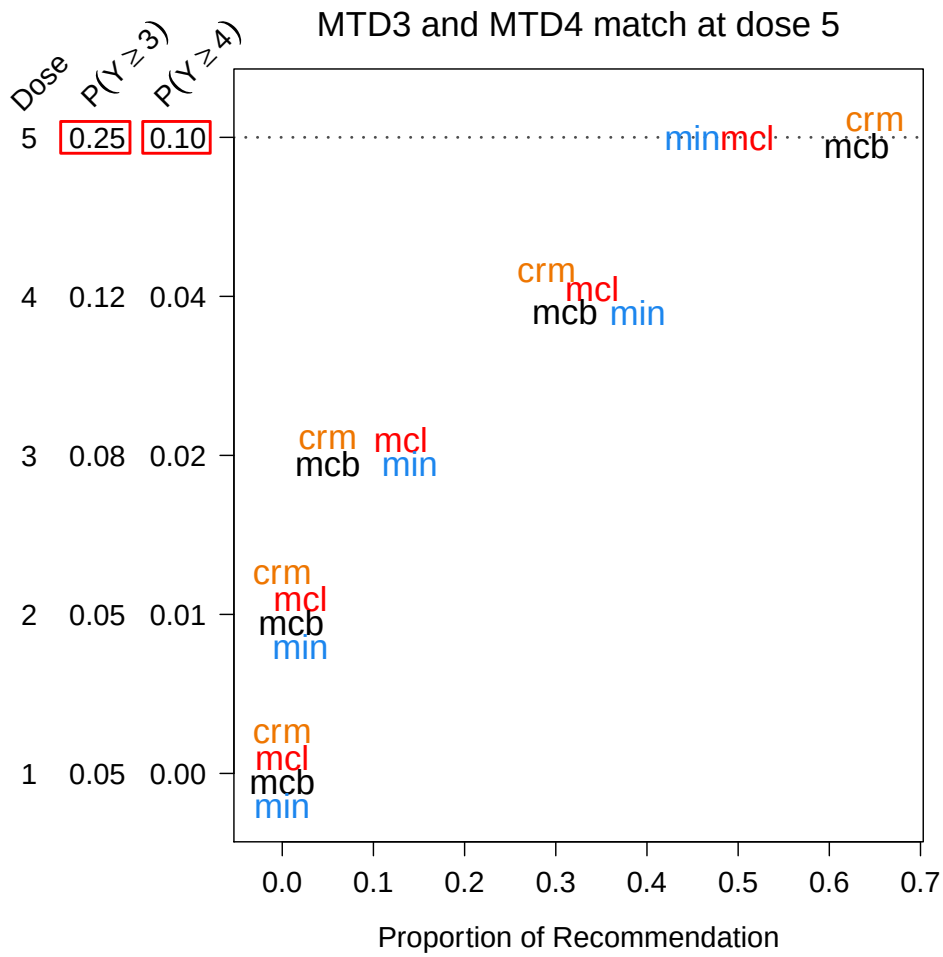
Grid search for optimal (δ_3, δ_4) pair



Results

Comparison of proposed method (MIN) to CRM, MCB, MCL





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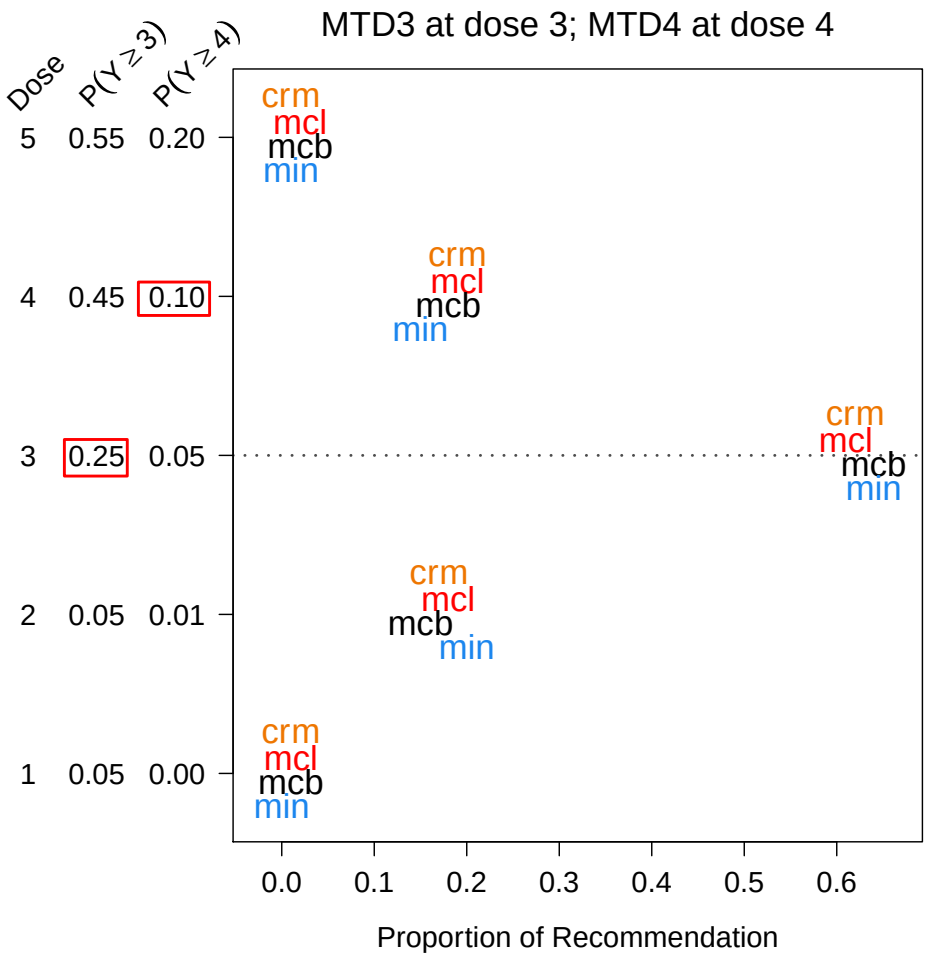

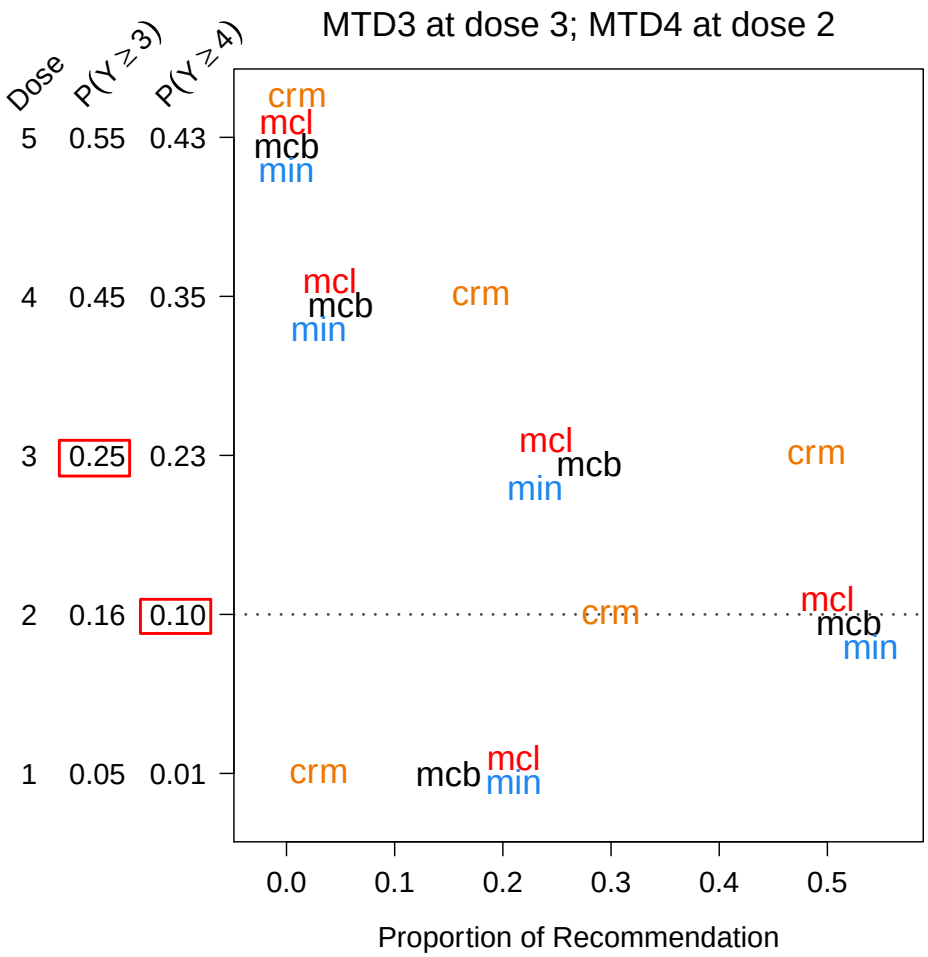

Conclusions

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

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