Early-phase Dose-finding Design for Molecularly Targeted Agents

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Outline

- Background
- Models & inference
- Dose-finding algorithm
- Simulation results
- Conclusions
Primary goal for a cytotoxic agent is to identify MTD

Recommended dose further investigated in Phase II to evaluate efficacy

Common assumption for cytotoxics is both efficacy and toxicity increase monotonically with dose

Recent development of molecularly targeted agents (MTA’s) challenges this assumption
Dose-finding For Molecularly Targeted Agents

- Toxicity may be minimal
  - Often reasonable to assume monotonicity
- Dose-efficacy curves may be non-monotonic
- Goal is to find optimal biological dose (OBD)
  - Defined by dose with acceptable toxicity that maximizes efficacy
Published Methods For MTA’s

- Hunsberger, Rubinstein, Dancey, Korn; *Statist Med* 2005
- Mandrekar, Cui, Sargent; *Statist Med* 2007
- Polley, Cheung; *Biometrics* 2008
- Hoering, LeBlanc, Crowley; *Clin Cancer Res* 2011
- Hoering, Mitchell, LeBlanc, Crowley; *Clin Trials* 2013
- Yin, Zheng, Xu; *Statist Med* 2013
Non-monotone Dose-efficacy Curves

- May exhibit unimodal or plateau relationships
  - Increase initially, then decrease or remain constant
- Suppose we have a set of I doses, \( \{d_1, \ldots, d_I\} \) and probability of efficacy at \( d_i \) is denoted, \( \pi_E(d_i) \)
- The goal is to find OBD, \( d_\nu \in \{d_1, \ldots, d_I\} \), defined by

\[
\pi_E(d_1) \leq \cdots \leq \pi_E(d_\nu) \geq \cdots \geq \pi_E(d_I).
\]
Possible Dose-toxicity/efficacy Curves

Yin, Zheng, Xu; Statist Med 2013
Phase I study of Bavituximab in patients with advanced solid tumors (Gerber et al.; Clinical Cancer Research, 2011)

Four available dose levels (0.1, 0.3, 1, 3 mg/kg)

Goal of the study was dose escalation to the OBD, rather than MTD

“...for monoclonal antibodies, the MTD may not correspond to optimal efficacy...”
Overall Strategy

- $d_\nu$ corresponds to the peak of unimodal curve or beginning of plateau
- Peak could occur at any of the $I$ available levels
  - Non-decreasing probabilities before the peak, non-increasing probabilities after peak
- Overall strategy is to formulate a set of possible dose-efficacy relationships corresponding to various “peak” locations
Possible Dose-efficacy Curves

1. monotone decreasing: peak at $d_1$
   $$\pi_E(d_4) \leq \pi_E(d_3) \leq \pi_E(d_2) \leq \pi_E(d_1)$$

2. monotone increasing: peak at $d_4$
   $$\pi_E(d_1) \leq \pi_E(d_2) \leq \pi_E(d_3) \leq \pi_E(d_4).$$

3. unimodal or plateau: peak at $d_2$
   $$\pi_E(d_1) \leq \pi_E(d_3) \leq \pi_E(d_4) \leq \pi_E(d_2)$$

4. unimodal or plateau: peak at $d_3$
   $$\pi_E(d_1) \leq \pi_E(d_2) \leq \pi_E(d_4) \leq \pi_E(d_3).$$
The probability of DLT at dose level $d_i$ is

$$\pi_T(d_i) \approx F(d_i, \beta) = p_i^{\exp(\beta)}$$

After $j$ inclusions, DLT probability estimates

$$\hat{\pi}_T(d_i) = F(d_i, \hat{\beta}_j)$$

define an acceptable set of doses based on a maximum acceptable toxicity rate $\phi_T$
Suppose there are $K$ dose-efficacy model possibilities under investigation.

For a particular model, $k$, the probability of efficacy modeled by

$$\pi_E(d_i) \approx G_k(d_i, \theta) = q_{ik}^{\exp(\theta)}$$

for a class of working dose-efficacy models, $G_k(d_i, \theta)$

$0 < q_{1k} < \cdots < q_{Ik} < 1$ represents the skeleton of model $k$. 
Inference

- Prior probabilities on each model $\tau(k) = \{\tau(1), \ldots, \tau(K)\}$ and prior distribution, $g(\theta)$, on $\theta$

- After inclusion of the first $j$ patients into the study, the likelihood under model $k$ is given by

$$L_k(\theta \mid D_j) = \prod_{\ell=1}^{j} \left\{ G_k(x_\ell, \theta) \right\}^{z_\ell} \left\{ 1 - G_k(x_\ell, \theta) \right\}^{(1-z_\ell)}$$

which, for each model, can be used in order to generate the posterior mean, $\hat{\theta}_{jk}$, of parameter $\theta$. 
The posterior probabilities of the models given the data are

\[ \omega(k \mid D_j) = \frac{\tau(k) \int L_k(\theta \mid D_j) g(\theta) d\theta}{\sum_{k=1}^{K} \tau(k) \int L_k(\theta \mid D_j) g(\theta) d\theta} . \]

When a new patient is to be enrolled, we choose a single model, \( k^* \), with the largest posterior probability such that

\[ k^* = \arg \max_k \omega(k \mid D_j) \]
Model Selection in CRM

- Bayesian model averaging CRM (Yin, Yuan; JASA 2009)
- Extended model-based designs for more complex dose-finding studies (O’Quigley, Conaway; Statist Med 2011)
- Posterior maximization and averaging for Bayesian working model choice in the CRM (Daimon, Zohar, O’Quigley; Statist Med 2011)
- CRM for partial ordering (Wages, Conaway, O’Quigley; Biometrics 2011)
Take the working model, $G_{k^*}(d_i, \theta)$, associated with $k^*$ to generate efficacy probability estimates at each dose.

Compute the posterior probability of a response for $d_i$

$$\hat{\pi}_E(d_i) = G_{k^*}(d_i, \hat{\theta}_{jk^*})$$

from which we can make decisions regarding allocation.
Overall, allocate the next entered patient to the dose estimated to be the most efficacious, among those with acceptable toxicity.

Define the set of “acceptable” doses as

\[ A_j = \{ d_i : \hat{\pi}_T(d_i) \leq \phi_T; i = 1, \ldots, I \} \].

The allocation algorithm depends upon the amount of data that has been observed so far in the trial.
Randomization Phase

- For doses in $A_j$, calculate a randomization probability $R_i$,

$$R_i = \frac{\hat{\pi}_E(d_i)}{\sum_{d_i \in A_j} \hat{\pi}_E(d_i)}$$

and randomize the next patient or cohort of patients to dose $d_i$ with probability $R_i$.

- Switch to a phase in which we simply allocate according to the maximum estimated efficacy probability among the acceptable doses.
Maximization Phase

Among the doses contained in $\mathcal{A}_j$, we allocate the $(j + 1)$th patient cohort to the dose $x_{j+1}$ according to the estimated efficacy probabilities, $\hat{\pi}_E(d_i)$, such that

$$x_{j+1} = \arg \max_{d_i \in \mathcal{A}_j} \hat{\pi}_E(d_i)$$

The optimal dose is the recommended dose $d_i = x_{n+1}$ for the hypothetical $(n + 1)$th patient after the inclusion of the maximum sample size of $n$ patients.
Design Specifications

- Skeleton for toxicity, $p_i = \{0.01, 0.08, 0.15, 0.22, 0.29, 0.36\}$
- Define maximum acceptable toxicity rate $\phi_T = 0.33$
- Total sample size $N = 48$
- Randomization phase sample size $n_R = 12$
- Each of the $k$ models has Normal prior distribution on $\theta$
  \[ g(\theta) \sim \mathcal{N}(0, 1.34) \]
Skeletons For Unimodal Relationships

- peak at $d_6[k = 1]$
  \{0.10, 0.20, 0.30, 0.40, 0.50, 0.60\}

- peak at $d_5[k = 2]$
  \{0.20, 0.30, 0.40, 0.50, 0.60, 0.50\}

- peak at $d_4[k = 3]$
  \{0.30, 0.40, 0.50, 0.60, 0.50, 0.40\}

- peak at $d_3[k = 4]$
  \{0.40, 0.50, 0.60, 0.50, 0.40, 0.30\}

- peak at $d_2[k = 5]$
  \{0.50, 0.60, 0.50, 0.40, 0.30, 0.20\}

- peak at $d_1[k = 6]$
  \{0.60, 0.50, 0.40, 0.30, 0.20, 0.10\}
Skeletons For Plateau Relationships

- plateau at $d_1[k = 7]$
  \{0.60, 0.60, 0.60, 0.60, 0.60, 0.60\}

- plateau at $d_2[k = 8]$
  \{0.50, 0.60, 0.60, 0.60, 0.60, 0.60\}

- plateau at $d_3[k = 9]$
  \{0.40, 0.50, 0.60, 0.60, 0.60, 0.60\}

- plateau at $d_4[k = 10]$
  \{0.30, 0.40, 0.50, 0.60, 0.60, 0.60\}

- plateau at $d_5[k = 11]$
  \{0.20, 0.30, 0.40, 0.50, 0.60, 0.60\}

- Assume, a priori, that each skeleton is equally likely and set $\tau(k) = 1/11$
Association Between Toxicity & Efficacy

- Association between toxicity and efficacy is ignored in modeling.
- Simulation studies assess the sensitivity of method to association between toxicity and efficacy.
- Correlated binary responses generated under various values of association parameter $\psi$.
- Results presented with $\psi = 4.6$ as in Hoering et al. (Clinical Trials, 2013).
Dose-finding in Hoering et al. (2013)

- 3+3 design in Phase I to find recommend dose (RD) for Phase II
- In Phase II, randomize 48 patients to one of three arms (dose levels)
  - RD−1, RD, RD+1
- Choose dose with highest efficacy that is also safe (DLT rate $\leq$ 33%).
- Authors define **best** dose as the level that maximizes efficacy while assuring safety; **good** dose as level where efficacy is above predefined boundary while maintaining safety.
Hoering et al. Scenarios

Possible Toxicity/Response Combinations

T1=(0.05, 0.1, 0.2, 0.28, 0.5, 0.5)

T2=(0.05, 0.1, 0.2, 0.28, 0.4, 0.55)

T3=(0.05, 0.1, 0.15, 0.2, 0.35, 0.4)

T4=(0.05, 0.05, 0.05, 0.05, 0.05, 0.05)

R1=(0.05, 0.13, 0.25, 0.38, 0.5, 0.63)

R2=(0.05, 0.23, 0.47, 0.7, 0.7)

R3=(0.7, 0.7, 0.7, 0.7, 0.7)
Simulation Results
Unimodal Dose-efficacy Curves

- **Scenario 1** ($\pi_T, \pi_E$)
  - $(0.05, 0.20), (0.10, 0.40), (0.25, 0.60), (0.45, 0.80), (0.60, 0.55)$
  - Peak of d-e curve occurs outside acceptable set

- **Scenario 2** ($\pi_T, \pi_E$)
  - $(0.08, 0.20), (0.12, 0.40), (0.20, 0.60), (0.30, 0.80), (0.42, 0.55)$
  - Peak of d-e curve occurs at edge of acceptable set

- **Scenario 3** ($\pi_T, \pi_E$)
  - $(0.06, 0.20), (0.08, 0.40), (0.14, 0.60), (0.20, 0.80), (0.30, 0.55)$
  - Peak of d-e curve occurs inside acceptable set
## Results

| True DLT prob. | 0.05  | 0.10  | 0.25  | 0.45  | 0.60  |
| True Eff prob. | 0.20  | 0.40  | 0.60  | 0.80  | 0.55  |
| % selection    | 0.04  | 0.19  | 0.53  | 0.24  | 0.00  |
| % allocation   | 0.12  | 0.26  | 0.35  | 0.23  | 0.03  |

| True DLT prob. | 0.08  | 0.12  | 0.20  | 0.30  | 0.42  |
| True Eff prob. | 0.20  | 0.40  | 0.60  | 0.80  | 0.55  |
| % selection    | 0.04  | 0.17  | 0.29  | 0.50  | 0.01  |
| % allocation   | 0.13  | 0.23  | 0.25  | 0.34  | 0.05  |

| True DLT prob. | 0.06  | 0.08  | 0.14  | 0.20  | 0.30  |
| True Eff prob. | 0.20  | 0.40  | 0.60  | 0.80  | 0.55  |
| % selection    | 0.04  | 0.13  | 0.19  | 0.62  | 0.03  |
| % allocation   | 0.10  | 0.19  | 0.20  | 0.43  | 0.07  |

\(N = 30; n_R = 10; \phi_T = 0.35, \psi = -2\)
Conclusions

- Bivariate extension of CRM for effectively estimating optimal dose in early-phase trials of targeted agents.
- Good operating characteristics when compared to published method in area.
- Extension includes relaxing monotonicity assumption for toxicity
  - For trials of dual-agent combinations
  - Use partial order CRM (Wages, Conaway, O’Quigley; Biometrics 2011) to estimate DLT probabilities
- Exploring stopping rules for toxicity and efficacy
- Modifications for delayed response outcomes
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