Bayesian Dose Escalation Study Design with Consideration of Late Onset Toxicity

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Outline

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- Methods
  - EWOC
  - EWOC-PH
  - Modifications to account for both DLT and long term toxicity

- Simulation Results

- Discussions and Recommendations
Introduction

- **Scope of phase I oncology trials**
  - Dose-limiting toxicity (DLT)
  - Maximum tolerated dose (MTD)
  - Standard design: 3+3

- **Bayesian adaptive designs**
  - Continual Reassessment Method (CRM; O’Quigley, et al., 1990)
  - Escalation with Overdose Control (EWOC; Babb et al., 1998)
  - Benefit: prior knowledge, available data from the trial, improved on target rate, better protection of patients
  - Limitations: not possible to account for late onset toxicity

- **Objective**
  - Account for both short term DLT and late-onset toxicity, with acceptable timeline
Dose Toxicity Model
--Binary endpoint

- Basic model: logistic regression

\[
\log it(p) = \log\left(\frac{p}{1-p}\right) = \log(\alpha) + \beta \log\left(\frac{d}{d^*}\right)
\]

![Dose-Toxicity Curve](image)
Based on the Bayesian logistic model, the posterior probability of DLT rate at each dose can be estimated.

MTD $\gamma$ is defined as the dose ($x$) at which a proportion $\theta$ (say 33%) of patients exhibit DLT, i.e.

$$P(DLT \mid x = \gamma) = \theta$$

EWOC Criteria: The dose for each subsequent patient will be selected so that the posterior probability that it exceeds the MTD is equal to 25% (a pre-specified feasibility bound).

MTD can be defined based upon the posterior probability density function of the MTD (can be based upon mean or median).
Escalation with Overdose Control (EWOC)
Decision based on Interval Probabilities

- Interval probabilities
  - Overdosing: DLT rate > 0.33
    - Overdose Criterion
      \[ \Pr(\text{DLT rate } p > 0.33) > 25\% \]
  - Targeted toxicity: DLT rate in (0.16, 0.33]
  - Underdosing: DLT rate < 0.16
  - Recommended Dose: 15 max target with overdose < 25%

Plot taken from Jaki and Hampson (2015)
Proposed by Tighiouart, Liu and Rogatko (2014) to account for late onset toxicity.

MTD $\gamma$ is defined as the dose at which a proportion $\theta$ of patients exhibit DLT during the observation window $[0, \tau]$, i.e.

$$P(T \leq \tau \mid x = \gamma) = \theta$$

The value chosen for the target probability $\theta$ depends on the nature and clinical manageability of the DLT.

- High when the DLT is a transient, correctable or non-fatal condition;
- Low when it is lethal or life threatening
The risk of DLT given dose is modeled using Cox proportional hazards model by assuming that patients given different doses of an agent have proportional risks of DLT.

\[ h(t \mid x) = h_0(t; u) \exp(\beta(x - X_{\text{min}})) \]

Model can be represented in terms of:

- \( \gamma = \text{MTD} \)
- \( \rho_0 = \text{probability of a DLT for a patient given dose } x = X_{\text{min}} \).
Any existing information about \( \gamma \) (MTD) and \( \rho \) (\( P(DLT|x=X_{\text{min}}) \)) can be reflected in the choice of their prior distributions

- Existing information could come from other clinical trials, published data, preclinical results, etc.
- Convenient parameterization since any existing information is likely to be most related to lower doses.

In the absence of prior information about the MTD (\( \gamma \)) and probability of DLT at \( X_{\text{min}} \) (\( \rho \)), independent vague priors can be selected for \( \rho_0 \) and \( \gamma \).

- For example, \( \rho_0 \sim \text{Unif}(0, \theta) \) and \( \gamma \sim \text{Unif}(X_{\text{min}}, X_{\text{max}}) \).
- Note these priors assume that the MTD must be between \( X_{\text{min}} \) and \( X_{\text{max}} \) and that the probability of DLT at \( X_{\text{min}} \) is no more than \( \theta \).

Probability of DLT will be estimated at 100% at \( X_{\text{max}} \) regardless of what any data will later say.

- Make sure \( X_{\text{max}} \) is higher than the highest dose that will ever be considered.
The k-th patient receives the dose $x_k$
- $x_k =$ dose at which the current posterior probability of exceeding the MTD is equal to the feasibility bound $\alpha$ (say, 25%).
- This is the overdose protection property of EWOC.

When the k-th patient enters the trial at time $t_k$, we calculate the posterior probability.

The time to event $Y_{i}$ is:
- time to DLT, if the patient experienced DLT.
- time since patient i was given dose $x_i$ (up to a maximum of $\tau$), if this patient is still at risk by this time (censored).

MTD can be defined based upon the posterior probability density function (pdf) of the MTD (such as median of posterior pdf of the MTD).
Time to Event EWOC-PH
--Modified Dose Recommendation

- Test pre-defined dose levels. Each cohort has at least 3 patients.
- Recommended dose for the next cohort decided when a minimum of 3 patients in the current cohort have been followed up for the DLT observation period.
  - The first patient in the cohort may have been followed for longer
  - Patients from previous cohorts also continued to be followed
  - No need to wait for the long term AESI to be resolved to enroll new patients, which can potentially reduce the trial length significantly.
- The Bayesian model based on EWOC-PH is used to estimate the probability of the long term AESI for each dose level.
  - The model will incorporate the available information on the long term AESI.
  - The risk of the long term AESI above the pre-specified toxicity level will be estimated.
    - Dose levels with estimated probabilities of long term AESI not greater than the pre-specified toxicity level (i.e. which meet the EWOC criteria) can be considered.
    - OK not to choose the highest possible dose.
In a phase I trial design, two Bayesian models are used: one for DLT and one for the long term AESI.

The probability of a DLT and the probability of the long term AESI are estimated for each dose level.

The dose may be selected if:

- the posterior probability of DLT has more mass in the targeted interval of 16-33% than any other dose and;
- the overdosing risk is controlled.
  - the risk of a DLT above 33% should not exceed 25%
  - the risk of a DLT above 60% should not exceed 5%
  - the risk of the long term AESI above 25% should not exceed 50%.
### Posterior Summaries--Example

--Estimated probabilities in each toxicity interval for each dose level

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>30</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DLT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below Target [0, 0.16]</td>
<td>0.87</td>
<td>0.80</td>
<td>0.60</td>
<td>0.37</td>
<td>0.21</td>
<td>0.13</td>
</tr>
<tr>
<td>On Target (0.16, 0.33]</td>
<td>0.12</td>
<td>0.19</td>
<td>0.34</td>
<td>0.46</td>
<td>0.45</td>
<td>0.37</td>
</tr>
<tr>
<td>Overdose (0.33, 1]</td>
<td>0.01</td>
<td>0.02</td>
<td>0.06</td>
<td>0.17</td>
<td>0.34</td>
<td>0.50</td>
</tr>
<tr>
<td>(0.6, 1]</td>
<td>0</td>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
<td>0.02</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Long term AESI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0.25, 1]</td>
<td>0.01</td>
<td>0.03</td>
<td>0.12</td>
<td>0.36</td>
<td>0.64</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Note that at dose = 80mg:

1. DLT mass above .33 is .17 < 25%; ✔
2. Long term AESI mass above .25 is .36 < 50% ✔
Recommended dose: 80mg

- Max target toxicity
- $P(DLT>0.33)<0.25$
- $P(AESI>0.25)<0.5$
Comparison with Traditional 3+3 Design

- Simulation studies were performed for various scenarios (a few listed below), and compared with the traditional 3+3 design.

<table>
<thead>
<tr>
<th>Scenario 1</th>
<th>Scenario 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prob of DLT</td>
<td>Prob of DLT</td>
</tr>
<tr>
<td>Prob of long term AESI</td>
<td>Prob of long term AESI</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Scenario 3</th>
<th>Scenario 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prob of DLT</td>
<td>Prob of DLT</td>
</tr>
<tr>
<td>Prob of long term AESI</td>
<td>Prob of long term AESI</td>
</tr>
</tbody>
</table>
Simulation Results
--Scenario 1

<table>
<thead>
<tr>
<th>Prob of DLT</th>
<th>Prob of long term AESI</th>
</tr>
</thead>
<tbody>
<tr>
<td>EWOC-PH 0.59</td>
<td>EWOC-PH 3+3 0.45</td>
</tr>
</tbody>
</table>
Simulation Results
-- Scenario 2

Prob of DLT

Prob of long term AESI

EWOC-PH

3+3

Prob of selection of a dose as MTD

Prob that a dose is tested

Prob of selection of a dose as MTD

Prob that a dose is tested
Summary of Simulation Results

- Compared to a traditional 3+3 design, the EWOC-PH design has more favorable operating characteristics with higher chance of selecting a dose within the target toxicity interval, and lower or similar chance of testing a dose above the target. Considerable improvements can be achieved if the long term AESI is important.
Discussions and Recommendations

- Simulation studies demonstrated the favorable operating characteristics of the EWOC-PH design with modifications compared to a traditional 3+3 design.

- The EWOC-PH design using a time to event toxicity endpoint can capture toxicity beyond the initial observation window and does not require waiting beyond the initial window.

- Trial length can be potentially cut considerably versus holding dose escalation until full observation of long term toxicities, given the importance of the late onset adverse event.
References

Thank you