PhUSE-SDE
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Mumbai

Shaping the Future of Drug Development

Novel designs in early phase Oncology studies

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Agenda

- Background - Dose escalation studies
- Challenges
- Dose escalation study designs
  - Rule based
  - Model based
- Bayesian Logistic Regression (BLR) design
  - Case study
  - Interpretation of results
- Highlights
Dose Escalation Studies

• Success rate of journey from phase I to FDA approval for Oncology drug molecule is the lowest (5.1% over timeframe 2006-2015)*

* Biotechnology Innovation Organization Report, June 2016
Dose Escalation Study- Oncology

Based on Presumption:
Efficacy and toxicity both increase with dose
Challenges: Dose Escalation Studies

- Investigational drug is examined in diseased patients; often suffering from advanced cancer

- Inability to distinguish between toxicity due to condition and toxicity due to drug

- Minimize the number of patients exposed to sub-therapeutic doses as well control severely toxic overdosing

- Use all available data efficiently

- Precisely estimating the MTD
Dose Escalation Study Designs

- Multiple approaches are proposed using DLT as the primary endpoint.
  - Rule-based designs
    - Utilize dose-escalation/de-escalation rules
    - Based on actual observations of target events (DLT) to assign patients to dose level
    - E.g. 3+3 design, accelerated titration design
  - Model-based designs
    - Estimate the MTD by estimating the dose-toxicity relationship
    - E.g. continual Reassessment Method (CRM), Bayesian Logistic Regression Model (BLRM), Escalation with overdose control (EWOC), modified Toxicity Probability Interval (mTPI)
Rule Based Design: 3+3 Study

- Pre specify a set of doses to consider, usually between 3 and 10 doses

- MTD is defined as the maximum dose at which fewer than one-third (< 33%) of subjects experience a DLT
Rule Based Design: 3+3 Study

• Most popular and widely used, costless implementation in practice

• Fixed cohort design

• Short memory, algorithm makes the decision

• Only recent cohort information and ignores data from earlier patients
Model Based Design: Bayesian Logistic Regression Model

- Described by Neuenschwander et al. (2008)
- Inference: Bayesian
- Based on a dose-toxicity model ~ 2 parameter logistic regression
- Prior: Based on historical data
- Posterior Distribution: Gather DLT data (binary) for each patient. Update the dose-toxicity rate model
- Following are intervals for probability of toxicity (DLT)
  - Under dosing toxicity: (0, 0.2]
  - Targeted toxicity: (0.20, 0.35]
  - Excessive toxicity: (0.35, 0.60]
  - Unacceptable toxicity: (0.60, 1.00]

12/6/2016
Dose Recommendation Using BLRM

- Posterior probability is calculated for all candidate doses

- The recommended dose is the one which maximizes the probability of being in targeted toxicity, while controlling the probability of excessive or unacceptable toxicity at 25%

  • Priority No. 1: target toxicity window
    Dose should maximize chance that DLT rate ∈ (20%, 35%)

  • Priority No. 2: overdose control
    Dose must have < 25% risk that DLT rate is > 35%

- BLRM implements the concept of escalation with overdose control
Case Study
First-in-human – Phase I Dose Escalation Study

**Primary Objectives**

- Evaluate the safety and tolerability of investigational drug in adult subjects with relapsed adenocarcinoma
- Determine the maximum tolerated dose (MTD) and/or biologically active dose (e.g. recommended phase 2 dose)
Study Design

- Multi-center, open-label, dose-escalation study
  Study has 2 parts

**Dose-escalation:**
- The dose-escalation will define the MTD, safety, tolerability, pharmacokinetic (PK) and pharmacodynamics (PD) of study drug

**Dose-expansion:**
- Dose-expansion will enroll additional subjects to gain further clinical experience with study drug

A final estimate of the recommended phase 2 dose will be based on BLRM using all subjects from dose escalation and expansion cohorts
Dose Escalation Phase

- Dose levels: 200, 400, 800, 1600, 3200, and 6400, 12800 µg/day
- 3-6 subjects per cohort
- Dose decision analyses performed after every cohort
  - Recommendation for subsequent doses is based on Bayesian model, the next dose is the one with
    - The highest probability of being in target interval (0.20, 0.35)
    - With a less than 0.25 probability of an excessive or unacceptable target interval

- Can incorporate intermediate dose levels
- The Dose Level Escalation Meeting is planned for dose level decisions
### Data for Ongoing Escalation Study

<table>
<thead>
<tr>
<th>Doses</th>
<th>200</th>
<th>400</th>
<th>800</th>
<th>1600</th>
<th>1600</th>
<th>3200</th>
<th>6400</th>
<th>12800</th>
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</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>3</td>
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<tr>
<td>No. of DLTs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*12/6/2016*
• Planned doses: 200, 400, 800, 1600, 3200, 6400 and 12800
• Intermediate doses: 4800, 9600
• Input data: subj dose response
• BLRM_Int: (0.2 0.35 0.60)
• BLRM_cut: (0 0.25 0.25)

<table>
<thead>
<tr>
<th>No of Subject</th>
<th>Dose</th>
<th>Response (DLT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>200</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>400</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>800</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>1600</td>
<td>1</td>
</tr>
</tbody>
</table>
## Results

<table>
<thead>
<tr>
<th>Dose</th>
<th>Prob (Target Toxicity)</th>
<th>Prob (Overdosing)</th>
<th>Centiles of probability of target toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.20-0.35</td>
<td>0.35-1</td>
<td>2.5%</td>
</tr>
<tr>
<td>200</td>
<td>0.0024</td>
<td>0</td>
<td>0.000084</td>
</tr>
<tr>
<td>300</td>
<td>0.0047</td>
<td>0</td>
<td>0.000216</td>
</tr>
<tr>
<td>400</td>
<td>0.0072</td>
<td>0.001</td>
<td>0.000411</td>
</tr>
<tr>
<td>600</td>
<td>0.0151</td>
<td>0.0006</td>
<td>0.000981</td>
</tr>
<tr>
<td>800</td>
<td>0.0269</td>
<td>0.0012</td>
<td>0.00169</td>
</tr>
<tr>
<td>1600</td>
<td>0.1143</td>
<td>0.0131</td>
<td>0.00694</td>
</tr>
<tr>
<td>3200</td>
<td>0.2711</td>
<td>0.1247</td>
<td>0.0221</td>
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<tr>
<td>4800</td>
<td>0.2998</td>
<td>0.27</td>
<td>0.0354</td>
</tr>
<tr>
<td>6400</td>
<td>0.2850</td>
<td>0.389</td>
<td>0.0459</td>
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<td>9600</td>
<td>0.2344</td>
<td>0.5446</td>
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<tr>
<td>12800</td>
<td>0.1944</td>
<td>0.6372</td>
<td>0.0736</td>
</tr>
</tbody>
</table>

12/6/2016
Next recommended dose is 3200 µg/day
- with probability of target toxicity interval as 0.2711
- with overdosing control as 0.1247 (<0.25%)

Statistician informs the highest dose level one may escalate to as per statistical analysis

Participants of Dose level escalation meet decide if synthesis of relevant clinical data justifies a dose escalation and to which dose (highest supported by the Bayesian analysis and protocol)
Highlights

• Next recommended dose is determined based on toxicity responses of all patients previously treated in the trial

• Evaluate intermediate doses in the trial

• Model tries to limit chances of overdosing

• Patient safety is the primary objective
  – Model quantifies knowledge about toxicity (DLT) data
  – Statistical inference serves as one component of a decision-making framework


• Phase 1 Trial Design: Is 3+3 the Best? A Hansen et. al. cancer control. Vol 21 (2014)
Thank-You

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