Model-based extrapolation between dosing regimens

Varying regimens in oncology Phase I dose-escalation trials

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Acknowledgements

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- Tim Friede
- Abdelkader Seroutou
Oncology Phase I Dose-Escalation

• Disease severity mandates efficacy maximization
• Aim is to find maximum tolerated dose (MTD)
• Adaptive trial design
  • Sequential enrollment of small cohorts of 3-6 patients
  • Treatment for 1 cycle
  • Assessment of cycle 1 trial data once cycle 1 completes
  • Dose of next cohort must ensure patient safety
• Challenges for statistical approaches
  • Data sparsity
  • (Drug combinations)
  • Only consideration of a dose escalation... Dose regimens??
Everolimus Example

- Phase Ib dose-escalation in small-cell lung cancer

- Explored two regimens
  - Daily dosing: 2.5 mg/day, 5.0 mg/day
  - Weekly dosing: 20 mg/week, 30 mg/week

- Each regimen analyzed separately

- MTD declared for daily 2.5 mg

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose [mg/admin]</th>
<th>N</th>
<th>DLT</th>
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<td>30.0</td>
<td>13</td>
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Bayesian Logistic Regression Model (BLRM)

- Statistical model
  - Data: # of patients with DLT $r_i$ per cohort with $n_i$ patients at dose $d_i$
  - Binomial likelihood with DLT probability $\pi_i(d_i)$
  - Logit-link regression: intercept, positive slope with $\log\left(\frac{d_i}{d^*}\right)$

- Escalation with overdose control (EWOC)
  \[ P(\pi(d) \geq 0.33) < 0.25 \]

- Regimens out of scope

- Ad-hoc limitations
  - Need for down-weighting $\Leftrightarrow$ efficiency loss
  - 2-step approach leads to one BLRM per regimen

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</table>

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Time to event pharmacokinetic model (TITE-PK)

- Time to first event model using an exposure metric
- Exposure metric based on drug pharmacokinetics
- Use of planned regimen and known PK parameters
TITE-PK model
Time-varying Poisson process

- Hazard at time $t$ proportional to exposure metric $E(t)$
  $$h(t) = \beta E(t)$$

  $$H(t) = \int_0^t h(t') \, dt' = \beta \text{AUC}_E(t)$$

  $$S(t) = P(T > t) = \exp(-H(t))$$

- Follow-up until time $t^*$ end of cycle 1
- Dosing regimen
  - Dose $d$
  - Frequency of dosing $f$
- EWOC metric for cycle 1 of a regimen
  $$P(T \leq t^* | d, f) = 1 - P(T > t^* | d, f)$$

  $$= 1 - S(t^* | d, f)$$
Everolimus Daily Regimen
Reanalysis Daily-\(\rightarrow\)Weekly Switch

- All models have matched priors
- Posteriors with daily data
- Posteriors with daily+weekly data
Everolimus Daily Regimen Reanalysis Daily->Weekly Switch

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[Graphs showing DLT probabilities across different doses for prior and posterior models]
Everolimus Daily Regimen
Reanalysis Daily->Weekly Switch

- All models have matched priors
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- Posteriors with daily+weekly data

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Conclusions

• Model based extrapolation
  • Enables more efficient use of trial data
  • Potentially enhances available historical data (collected under different regimens)
  • Requires assumptions here: Pharmacokinetic principles

• Advantages of TITE-PK
  • No more need for ad-hoc approaches used to combine different dosing regimens ⇔ easier to apply + greater statistical efficiency
  • Greater flexibility for escalation trials
  • Coherent (single-model) dose-toxicity model for multiple regimens
  • Operationally feasible
Thank you
References

