Bayesian modelling for combination dose-escalation trial that incorporates pharmacokinetic data

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Topics covered

- Rationale for novel modelling approach
- Bayesian dose exposure model
  - Definition
  - Integration into dose-escalation decision process
- Robust prior derivation
- Implementation in PhI studies at Novartis
- Conclusion
Background

- PhIIb combination dose-escalation trials: both drugs may be novel, both drugs may be escalated

- Two types of drug-drug interactions (DDI)
  - **Safety DDI:**
    - Increased/decreased DLT rate from that expected as monotherapy
    - BLRM models dose-DLT relationship and estimates safety DDI
  - **PK DDI:** exposure of one or both drug(s) are increased/decreased from that expected as monotherapy
  - Link between PK DDI and safety DDI can be complex
    - PK DDI may explain only parts of overall safety DDI
    - Safety DDI can be seen without PK DDI

- How to incorporate PK information in a robust way into dose escalation decision?
Bayesian dose-DLT model

Current use of PK data for dose selection

PK data are already used in the decision
Adding Bayesian dose-exposure models

New use of PK data for dose selection

Bayesian dose-DLT model
(safety DDI)

DLT rate prior

DLT rate posterior

DLT escalation rules

Model recommended dose

Other PK data

Other data

Clinical expertise

Bayesian dose-exposure models
(PK DDI)

Exposure prior

Dose-exposure data

Exposure posterior

Exposure escalation rules

Dose escalation decision
Evolution in dose-escalation paradigm

- New primary objective: identify ‘safe’ dose with desired exposure
- Combine outputs from independent modeling of dose-DLT and dose-exposure relationships to establish MTD/RDE with optimal exposure of both agents
- Safety comes first! Highest doses allowed by Bayesian Logistic Regression Model (BLRM) following Escalation With Over-dose Control (EWOC) principle to control risk of over-toxicity
- Desired exposure driven by safety, pharmacodynamic and clinical activity (especially true for new targeted therapies with safer profile)
- Feasible since PK measured in all trials. Can be tailored to more complex settings
- Doesn’t prevent escalation to proceed on the basis of safety data only (when PK data not available and not critical for next decision)
Added value of integrating dose-exposure modelling

*Simulation study [details in Cotteril (2015)]*

- **Decrease subjectivity** of its use
- **Increase efficiency** of decision process
  - Escalation paths more varied and escalation of both drugs more likely
- **Increase precision** of the resulting dose recommendation
  - Less dose pairs declared as the final recommended dose
- **Minimise** number of patients treated at **sub-optimal dose levels**
  - Escalation faster when negative DDI
- **Minimise** number of patients **overdosed**
  - Escalation more cautious when positive DDI
One BLRM + two dose-exposure models

- 5-parameter BLRM for combination is used [Neuenschwander (2014)]
- Empirical bayesian dose-exposure model for each compound A and B:

\[
\log(pkA_{dA, dB}) = \phi_1A_{(dB=0)} + \phi_2A \log(dA/dA^*) + \phi_3A_{(dB>0)} + \phi_4A \log(1+dB/dB^*) + \epsilon_A
\]

\[
\log(pkB_{dA, dB}) = \phi_1B_{(dA=0)} + \phi_2B \log(dB/dB^*) + \phi_3B_{(dA>0)} + \phi_4B \log(1+dA/dA^*) + \epsilon_B
\]

\[
\epsilon_A \sim N(0, 1/\tau_A^2)
\]

\[
\epsilon_B \sim N(0, 1/\tau_B^2)
\]
Defining target exposures

- Define target exposures $T_A$ and $T_B$: typically exposures at s.a. RP2Ds but could be lower (e.g. if indicated by preclinical studies)

- Define relevant posterior summaries for each combination of interest:
  - Median exposures (with probability intervals)
  - Distance between posterior distribution of exposures and target exposures
    \[
    g_h = \sqrt\left(\frac{T_A - pkA_h(d_A, d_B)}{1/\tau_{A_h}}\right)^2 + \left(\frac{T_B - pkB_h(d_A, d_B)}{1/\tau_{B_h}}\right)^2
    \]
    
    \[
    g = \frac{\sum_{h=1}^H g_h}{H} \quad \text{For } H \text{ iterations of MCMC;}
    \]
  - Probabilities of under/over exposure, e.g.
    \[
    p = P(pkA(d_A, d_B) \in [T_{A_{low}}, T_{A_{high}}] \text{ and } pkB(d_A, d_B) \in [T_{B_{low}}, T_{B_{high}}])
    \]
Defining target exposures (cont.)

- Identify ‘safe’ combinations (as per EWOC) that allow to reach predefined target exposures for both drugs (as per metrics chosen).

- If there is too much uncertainty about target exposure, better not to use target exposure. Instead rely on estimates to learn about interaction.
Illustration after 1 cohort of 3 patients with large DDI

<table>
<thead>
<tr>
<th>Drug A (mg)</th>
<th>50</th>
<th>100</th>
<th>200</th>
<th>300</th>
<th>400</th>
<th>500</th>
<th>600 (s.a RP2D)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Starting dose

Smallest distance

Target when no PK DDI

<table>
<thead>
<tr>
<th>Recommended next dose based on BLRM (mg) A/B</th>
<th>Posterior probability of the BLRM recommended next dose</th>
<th>Estimated exposure (ng*h/ml) 90% probability interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Underdose [0%,16%]</td>
<td>Target toxicity [16%,35%]</td>
</tr>
<tr>
<td>200/300</td>
<td>0.3998</td>
<td>0.4387</td>
</tr>
<tr>
<td>100/450</td>
<td>0.3672</td>
<td>0.4817</td>
</tr>
</tbody>
</table>
Prior building and robustification

- A 4-step approach to combine all sources of prior information

- Step 1: leverage single agent data (+ relevant combination data)
  - Fit bayesian models (using non-informative priors) to obtain informative priors for s.a. parameters $\phi_1$, $\phi_2$ and for inter patient variability $\varepsilon$
  - Non-informative priors obtained for parameters related to DDI
  - Down-weight posterior variances so that effective sample size corresponds to moderate/substantial heterogeneity between historical data and on-study data (meta-analytic-predictive prior can also be used)
  - PK information may only be available in external publication as summary statistics
Prior building and robustification (cont.)

- Step 2: integrate DDI predictions from PB/PK modelling:
  - Simcyp is a population-based simulator:
    - Incorporates numerous databases containing human physiological, genetic and epidemiological information.
    - Allows to integrate this information with in vitro and clinical data to predict PK behavior in ‘real-world’ populations.
  - Used to adapt parametrization of empirical Bayesian model to likely mechanism of DDI
  - Build informative priors for all parameters, including those related to DDI: $\varphi_3$, $\varphi_4$ and also $\epsilon$
    - Use PB/PK model to simulate pkA and pkB for virtual patients
    - Fit bayesian models on pkA and pkB (using non-informative priors)
    - Down-weight posterior variances so that effective sample size corresponds to substantial/large heterogeneity between PB/PK DDI predictions and DDI in trial population
Prior building and robustification (cont.)

- **Step 3:** build a non-informative (NI) prior for all parameters:
  - Same as Simcyp prior but with further down-weighting so that effective sample size corresponds to one observation

- **Step 4:** combine 3 priors in a mixture that provides good behavior to the model even when conflict between prior and data
  - Define prior weights, e.g. 0.4, 0.4 and 0.2 for SA, Simcyp and NI priors, respectively
  - Prior weights are updated into posterior weights when model is updated with data
Illustration of mixture prior

Mixture for dose-independent DDI parameter

Posterior weights when data aligned with Simcyp prior
prior weights: 0.4(SA), 0.4(Simcyp), 0.2(NI)
Implementation in protocol

- Selected PK parameters are co-primary or key secondary endpoints

- Flexible wording regarding the recommendations provided by the Bayesian dose-exposure model

- Estimated exposures provide additional information to further guide the dose selection

- No additional constraint on the dose escalation:
  - For later cohorts, the dose escalation may occur without having the full PK data available, on condition that the EWOC criterion is met
  - Higher escalation step allowed when negative PK DDI
5 combinations trials:
- Combination treatment where significant PK DDI is expected
- PK data of single agent studies available
- Bayesian model parametrization can be tailored to design features (e.g. when s.a. PK run-in is added)

1 single agent trial:
- Limited toxicity anticipated + RP2D should have similar exposure than competitors

No challenge from HA and IRBs so far
Concluding remarks

- **Evolution** from current dose-escalation paradigm since the identification of the RDE/RP2D gives more weight to non-DLT data

- Current approach benefited from **cross functional collaboration** (biostatistics, clinical pharmacology, drug metabolism & pharmacokinetics, clinical)

- Requires an **early and close collaboration** at project team level
  - DDI risk should be discussed and addressed early in protocol concept

- Requires more time to set up but lead to design with **increased efficiency**

- Method is still novel and adaptations are expected from learnings during execution phase of trials
References


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