Model-informed Approaches to Support Dosage Selection in Pediatric Patients

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Outline

• Highlight the ongoing challenges in identifying appropriate dosing regimens for pediatric patients across a wide age spectrum from newborns to young adults.

• Overview model-informed precision dosing approaches in support of designing and expediting oncology drug development in pediatrics.

• Describe examples of the application of model-informed approaches to support dosage selection of oncology drugs in pediatric patients.
Why model-informed dose selection in pediatrics?

- Children are not small adults
- Rapid growth and development (maturation) in size and organ functions impact drug response
- Clinical PK/PD data are limited in children
- Large inter-patient variability
- “One size does not fit all”
- To better predict and control exposure and response in pediatric population and individual patients


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Model-informed precision dosing (MIPD)

- Gender, Age, Body size
- Pharmacogenes
- Lab results Kidney/Liver function

PK/PD model → Tailored starting dose → Dose adjustments → Precision dosing

Drug concentrations Lab results PD biomarkers
Model-informed approaches to support dose selection and clinical trial design in pediatric drug development

Extrapolation from adults to children

Simulation using pediatric models

Identify age-appropriate dosing regimens

Determine optimal time points and sample size

Confirm results with simulations

Population PK modeling

Pediatric PK modeling

Monte Carlo Simulations

Dose selection by exposure matching

Trial design

Phase I Study

- Prior knowledge
- Rich adult PK data in healthy volunteers/patients
- Incorporation of covariates
- Individual PK simulation in realistic age-matched population
- Age-appropriate doses to match adult exposures
- Sample size and power evaluation
- D-optimal sampling design
- Conduct Phase I clinical trial
- Confirm results with simulations

Case study 1

Model-informed pediatric dose selection for sirolimus in infants with vascular tumors and malformations
Implications of maturation on drug response in infants

Neonates and infants experience rapid physiological changes in their organ function, in addition to the growth in body size.
Effect of body size and maturation on sirolimus clearance in children

Sirolimus clearance estimated using Phase 2 clinical trial for pediatric patients with vascular tumors and malformations

- Increased sirolimus clearance in older children can be described using allometrically scaled body weight (growth of body size)
- There is a rapid maturation in clearance in younger children <2 years old
- Need to optimize dosing regimens in young children

Development of a model to describe clearance maturation in young children

Maturation model

\[ CL_{\text{pediatric}} = CL_{\text{adult}} \cdot \left( \frac{BW}{70} \right)^{0.75} \cdot MF \]

\[ MF = \frac{PMA_{\text{Hill}}}{TM_{50}^{\text{Hill}} + PMA_{\text{Hill}}} \]

Clinical trial simulations to identify age-appropriate dosing regimens


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Clinical trial simulations to identify age-appropriate dosing regimens to optimally achieve target attainment


Designed dosing regimen

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Dosing regimens (mg/m² BID)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1 months</td>
<td>0.4</td>
</tr>
<tr>
<td>1–2 months</td>
<td>0.5</td>
</tr>
<tr>
<td>2–3 months</td>
<td>0.6</td>
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<tr>
<td>3–4 months</td>
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<td>6–9 months</td>
<td>1.1</td>
</tr>
<tr>
<td>9–12 months</td>
<td>1.3</td>
</tr>
<tr>
<td>12–24 months</td>
<td>1.6</td>
</tr>
</tbody>
</table>

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Clinical trial of sirolimus in infants with tuberous sclerosis complex

- The developed age-appropriate dosing regimens have been used as the initial dose for all participants
- Subsequent dose is adjusted based on concentration measurements with Bayesian estimation
Physiologically based pharmacokinetics (PBPK) modeling
Developmental changes in sirolimus clearance

PBPK model-based simulations
n= 400 virtual pediatric subjects

Observations (Bayesian estimates)
316 data from 24 patients

Maturation model

\[ CL_{\text{pediatric}} = CL_{\text{adult}} \cdot \left( \frac{BW}{70} \right)^{0.75} \cdot MF \]

\[ MF = \frac{\text{PMA}_{\text{Hill}}}{\text{TM}_{50,\text{Hill}} + \text{PMA}_{\text{Hill}}} \]

Allometric scaled clearance (L/h/70 kg)

Postmenstrual age (weeks)

Birth 1 year 2 years 4 years
Case study 2

Population PK/PD modeling and ER analysis of mirdametinib in adolescents and adults with neurofibromatosis type-1 (NF1) related plexiform neurofibromas (PN)
NF1-related PN and MEK inhibitor mirdametinib

- Plexiform neurofibromas (PNs) are nerve sheath tumors that develop in ~40% of patients with neurofibromatosis type 1 (NF1).¹,²

- PNs are associated with morbidities and complications such as severe pain, disfigurement, reduced quality of life, and malignant transformation.¹-³

- Mirdametinib is an investigational oral MEK1/2 inhibitor that was evaluated in the Neurofibromatosis Clinical Trials Consortium Phase 2 NF106 clinical trial (NCT02096471) in adolescents and adults with NF1-PN.¹

Data obtained from Phase 2 (NF106*) study

PK/PD Modeling

Clinical trial simulations

Exposure (AUC) simulations

Tumor growth simulations

In silico Exposure-response (ER) analyses using simulated data

AUC vs. Tumor volume

Dose vs. Probability of response

Virtual population sampled from NHANES database

Adapted existing integrated popPK model in adults for NF106 population

*NF106 study: Neurofibromatosis Clinical Trials Consortium Phase 2 clinical trial in adolescents and adults with NF1-PN (NCT02096471).
Mirdametinib PK/PD model development using tumor growth inhibition (TGI) modeling

PK/PD model structure

PK

Oral dose

Vp1/F

Q1/F

Ka

Kg

Tumor growth rate

Vc/F

Tumor volume (mL)

Vp2/F

Q2/F

CL/F

PD (TGI)

K_{Drug} \cdot AUC \cdot e^{\lambda t}

Drug effect

Effect of age on tumor growth rate

No age effect within the age range of the NF106 study (16-39 y)

1Akshintala et al. Neuro Oncol. 2020
Simulations of tumor growth profile for various dosing regimens

Unpublished data
ER relationship between AUC and tumor volume

Unpublished data
ER relationship between dose and probability of response (≥20% tumor volume reduction)

Unpublished data
Summary- mirdametinib case study

- Mirdametinib PK/PD model has been successfully developed by linking drug exposure and dynamic tumor volume changes.

- ER relationship was characterized by clinical trial simulations using the developed TGI model.

- Safety data (i.e. risk of adverse drug reactions) and the exposure-response for safety relationship should be considered to determine the optimal dose and/or regimen.

- Developed modeling and simulation framework will provide a foundation and could help in the design of future studies.
Conclusion

• Drug disposition and response in pediatric patients can be described with a quantitative pharmacometric approach by considering growth and maturation.

• Model-informed precision dosing is feasible and helpful in supporting dose selection in pediatric patients.

• Multidisciplinary collaboration and integration of advanced technologies are essential to facilitate the implementation of model-informed precision dosing.
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