Modelling the interaction between Irinotecan and efflux transporters inhibitors : A KPD tumour growth inhibition model including interaction components

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Introduction

- ATP Binding Cassette (*ABC*) transporters play an important role in anticancer drug resistance.
- Breast Cancer Resistance Protein (*BCRP*) is an ABC transporter involved in the efflux of a wide range of substrates such as Irinotecan (*CPT-11*) and its active metabolite SN38. BCRP is thus involved in CPT-11 resistance.
- MBLI87, a new BCRP inhibitor, has shown high activity against BCRP efflux in *in vitro* studies[1] and also against CPT-11 BCRP mediated resistance in xenografted mice[2].

Objectives

To model the interaction between BCRP inhibitors and CPT-11 in SCID mice with CPT-11 resistant xenografts
To compare MBLI87 effects with the BCRP reference inhibitor, gefitinib against CPT-11 BCRP mediated resistance

Data

- 60 SCID mice were inoculated with CPT-11 resistant or non resistant tumour cells at each flank
- Mice received drugs during a 2-week period followed by a 2-week rest period during 8 weeks
- 6 treatment arms : Control, CPT-11, Gefitinib, MBLI87 CPT-11+Gefitinib, CPT-11+MBLI87
- Tumour measurements (length and width) were assessed every 2 days after the 1st drug administration
- Geometric mean of the 4 measures (length, width on each flank) was calculated for each measure

⟶ Geometric mean : Dependent Variable

Methods

- 2 families of model were tested :
  - Interaction models (Minto[3], Greco[4])
  - Tumour growth inhibition (*TGI*) models (Claret[5], Simeoni[6])
- Some modifications were added to the TGI models :
  - **A K-PD[7] model** was used to describing drug kinetics Drug effects were dependant on the amount of drugs
  - **An interaction parameter** was added to quantify the action of BCRP inhibitors on CPT-11 cytotoxic effect
- Model parameters were estimated by the FOCE method (NonMem VI)

Results

Interaction models

- Only one dose level is tested : Not possible to describe surface response as proposed by Minto
- Greco approach did not allow to describe properly tumour growth

⟶ "Interaction models" were rejected

Tumour growth inhibition models

- Simeoni was preferred to the Claret model based on OFV and AIC values
  - Simeoni model : AIC = -453.0
  - Claret model : AIC = -440.2
- Final model is **a modified Gompertz tumour growth inhibition model with K-PD and interaction components :**
  - CPT-11 effect is related to the amount of drug in the kinetic compartment
  - BCRP inhibitors modifies CPT-11 activity

Final Model Equations

$$\frac{dA_X}{dt} = -K_{e,X} * A_X$$

$$\frac{d\phi_{tumour}}{dt} = \frac{\lambda_0 * \phi_{tumour}}{(1 + (\frac{\lambda_0}{\lambda_1} * \phi_{tumour})^{\psi})^{\frac{1}{\psi}}} - K_{2,X} * DR_X * \phi_{tumour}$$

$$DR_X = K_{e,X} * A_X$$

X: CPT-11, gefitinib,MBLI87

In case of joint administration, K2 parameter accounts for the effect of MBLI87 and gefitinib on CPT-11 cytotoxic effect

$$K_{2,CPT-11} = K' + K'' * DR_{Inhibitors}$$

Inhibitors: gefitinib,MBLI87

A : Drug amount with a constant elimination rate K_e
λ_0, λ_1 : Gompertz parameters describing tumour growth
Ψ: Exponential to linear phase switch parameter
K_2 : Drug potency parameter
K '': Interaction parameter

Final Model Evaluation

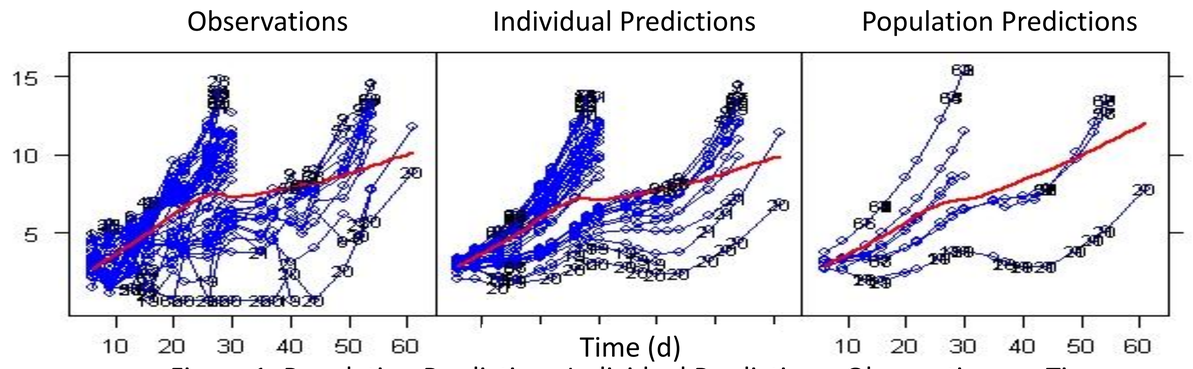

Figure 1: Population Predictions Individual Predictions, Observations *vs* Time
Blue lines: Observations, Predictions Red lines: Trend line

Individual Predictions plot show good model performances

Parameter Estimates

Parameter	Typical Value	%IIV
λ_0 (d^{-1})	0.06	33
λ_1 ($mm.d^{-1}$)	0.2	46
$K_{2,\ CPT\text{-}11}$ (mg^{-1})	0.3	-
$K_{2,\ Gefitinib}$ (mg^{-1})	10^{-2}	-
$K_{2,\ MBLI87}$ (mg^{-1})	10^{-2}	-
$K''_{\ CPT\text{-}11,Gefitinib}$	10^{-2}	-
$K''_{\ CPT\text{-}11,\ MLBI87}$	5.3	-

Table 1: Parameter Estimates

- Potency of BCRP inhibitors are estimated at 10^{-2} mg^{-1}

⟶ BCRP inhibitors alone have no effect

- **A significant synergistic effect is found between MBLI87 and CPT-11 (K''=5.3)**
- None is found with gefitinib (K''=10^{-2})
- There is no difference in tumour size kinetics between these both cohorts, model confirms that interaction is stronger between MBLI87 and CPT-11

Conclusion

- Results **show that MBLI87 is able to revert CPT-11 resistance at a 20-fold lower dose compared to gefitinib**
- Future use of the model will be optimizing a dose finding study in mice

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