Population Based Pharmacodynamics for In Vitro Drug Sensitivity Assays: Prediction of Model Based Parameters of Drug Activity and Relationship to Clinical Outcome

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Introduction

Patient samples give limited amounts of cells for in vitro drug sensitivity assays. Yet it is desirable to obtain information on concentration-response relationship in the individual tumor as such estimates may be of value of predicting clinical response to drug therapy.

Objectives

1. To develop a population PD model for the in vitro drug sensitivity of leukemic cell samples from patients with acute myelocytic leukemia (AML) for cytosine arabinoside (AraC) and daunorubicin (Dnr).
2. To relate estimated individual in vitro parameters to clinical outcome.

Material and Methods

- ✓ Tumor cell samples from 179 patients with AML (n_{obs}=1085).
- ✓ Fluorometric microculture cytotoxicity assay.
- ✓ 1-5 concentrations of each drug was tested, ranging 0.02-12.5 µg/ml for AraC and 0.004-12.5 µg/ml for Dnr.
- ✓ Estimation method: FOCE in NONMEM V.
- ✓ Population PD model
  - × Model development was based on 124 patients (n_{obs}=704).
  - × External evaluation was based on 30 patients (n_{obs}=300).
- ✓ Probability of clinical outcome
  - × 46 patients treated with the AraC+Dnr combination.
  - × A logistic regression model.
  - × Estimated individual pharmacodynamic parameters from in vitro assay was used to predict clinical outcome.

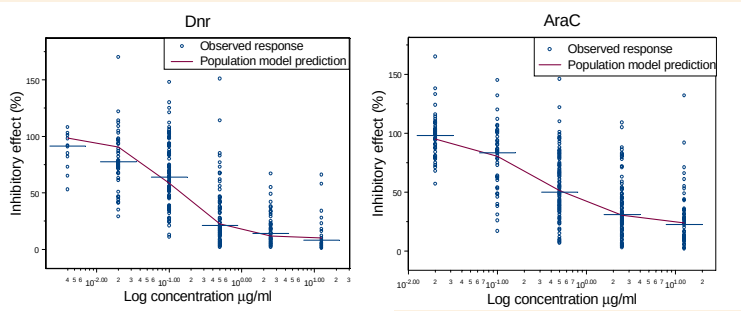

Figure 1. The observed inhibitory effect at different concentrations of AraC (left) and Dnr (right) and corresponding population model prediction (solid line).

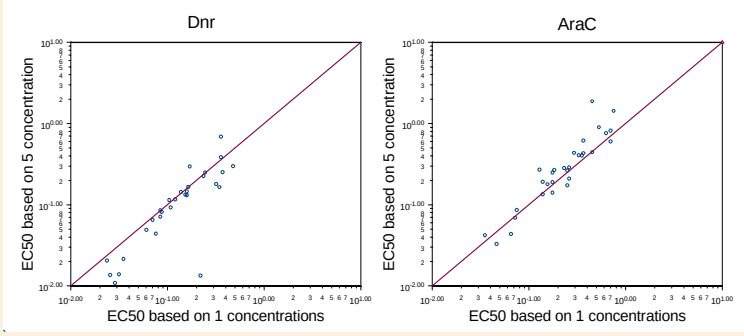

Figure 2. Bayesian estimations of EC50 based on one versus five effect-concentration measurements of the evaluation dataset for AraC (left) and Dnr (right). The single concentration used was 0.1 µg/ml for both drugs.

Results

- ✓ PD-model
  - ×AraC: Emax model and Dnr: Sigmoid Emax model
  - ×High correlation between Emax for the two drugs.
- ✓ EC50 could be predicted from only one concentration.

		Dnr	AraC
Typical value (RSE %)	Emax	90% (2.4)	78% (3.5)
	EC50	0.11 µg/ml (15)	0.30 µg/ml (15)
	Slope	1.23 (13)	1 FIX
Interindividual variability	Emax (10-90%)	74-96 %	35-93 %
	EC50 (10-90%)	0.022-0.57 µg/ml	0.098-0.82 µg/ml
Correlations	$Emax_{Dnr}$-$Emax_{AraC}$	0.72	
	$EC50_{Dnr}$- $EC50_{AraC}$	0.4	

Table 1. The estimated pharmacodynamic parameters for Dnr and AraC, respectively. The population mean parameters is presented with the relative standard error (RSE%). The variability in individual EC50 and Emax are presented as the 10% and 90% percentile.

- ✓The probability of clinical response was best and significantly ($p<0.05$) related to the product of the ratio of individual Emax to EC50 of the two drugs.

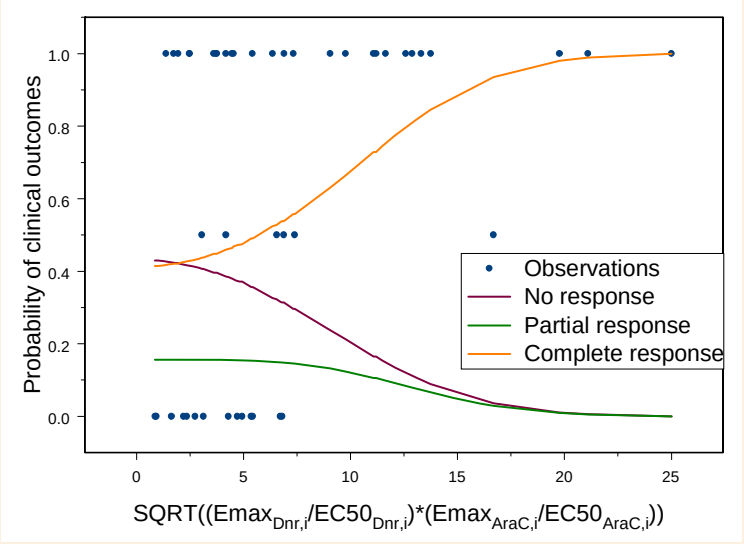

Figure 3. The estimated probability of complete, partial or non response versus the product of the respective ratios of individual Emax to EC50 of AraC and Dnr (solid lines). For illustration the observed clinical response is inserted at 1, 0.5., 0 for complete, partial and non response respectively (dots).

Conclusions

- ✓ A joint pharmacodynamic model for AraC and Dnr including covariances across drugs, could adequately describe the in vitro sensitivity data.
- ✓ Drug potency could be obtained even with sparse sensitivity measurements.
- ✓ The model for clinical outcome is mechanistically reasonable and supports the dual therapy.