PK/PD model of indisulam in combination with capecitabine

a time-dependent pharmacokinetic interaction contributes to excessive hematological toxicity

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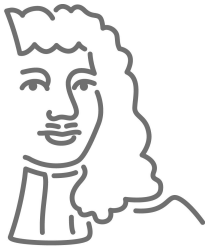


Outline

- Clinical study
- Hypothesis
- Aims
- Model development
- Simulation studies
- Conclusions
- Clinical recommendation

Clinical study

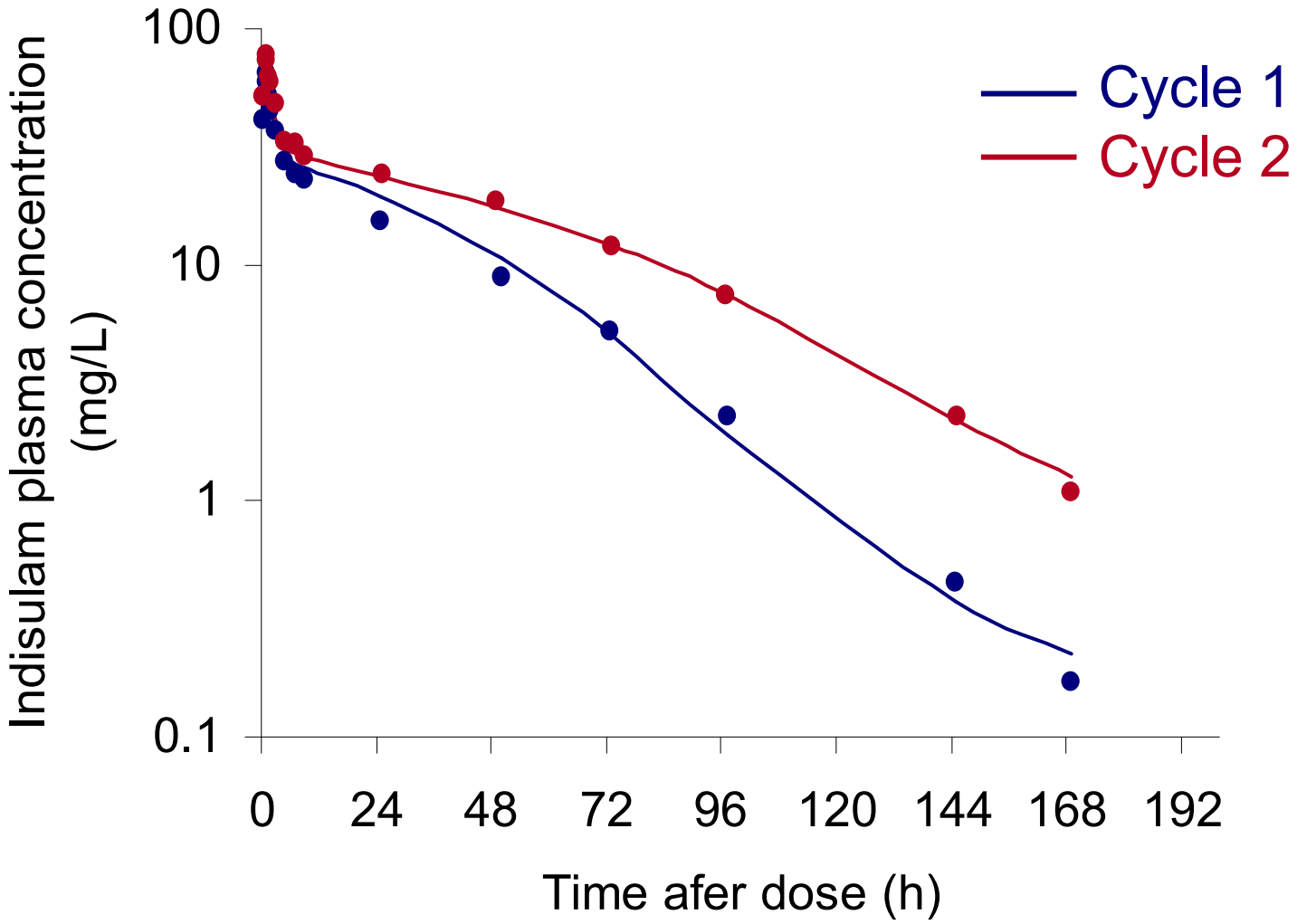
- Phase I dose escalation study of indisulam in combination with capecitabine
- 1-hour infusion indisulam day 1 and

  oral capecitabine BID on days 1-14
- Dose escalation: 350 -800 mg/m^2 indisulam / 1000 –1250 mg/m^2 capecitabine BID

Clinical study

- Cycle 1 was well tolerated
- Severe side effects at cycle 2
- Increased exposure to indisulam at cycle 2

Increased exposure to indisulam

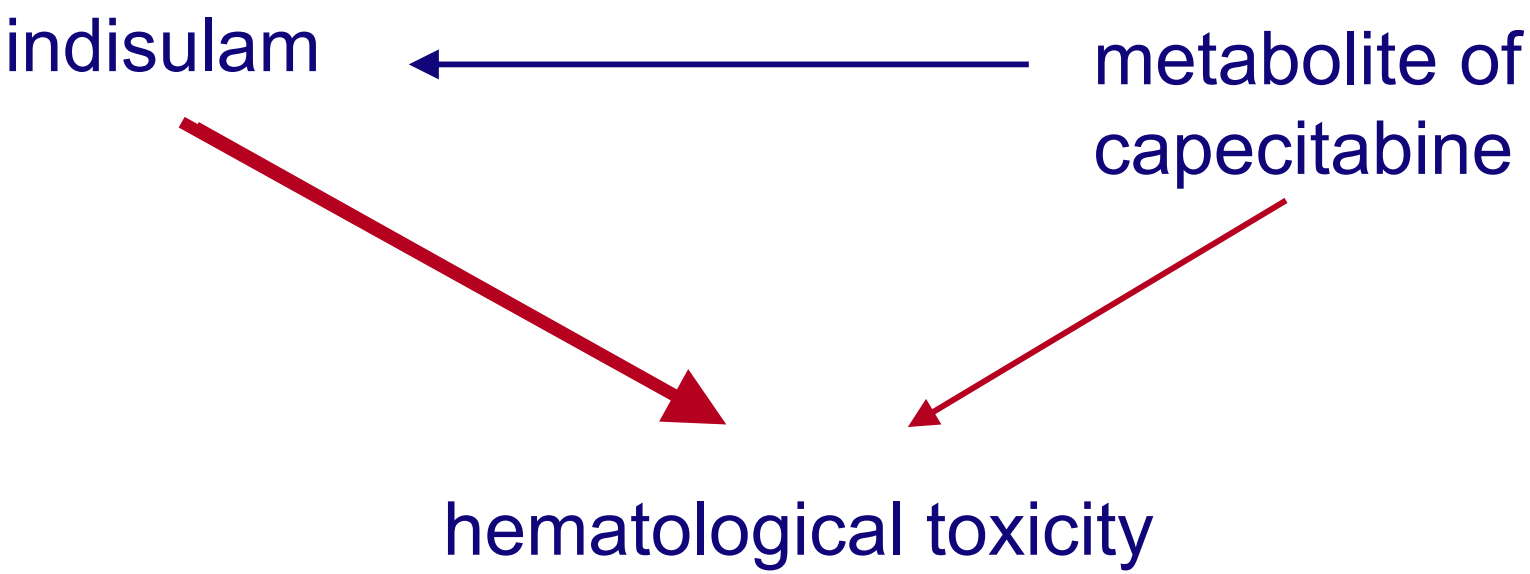


Hypothesis

- Time-dependent drug-drug interaction?
- (A metabolite of) capecitabine may inhibit the synthesis of CYP2C9

Hematological toxicity

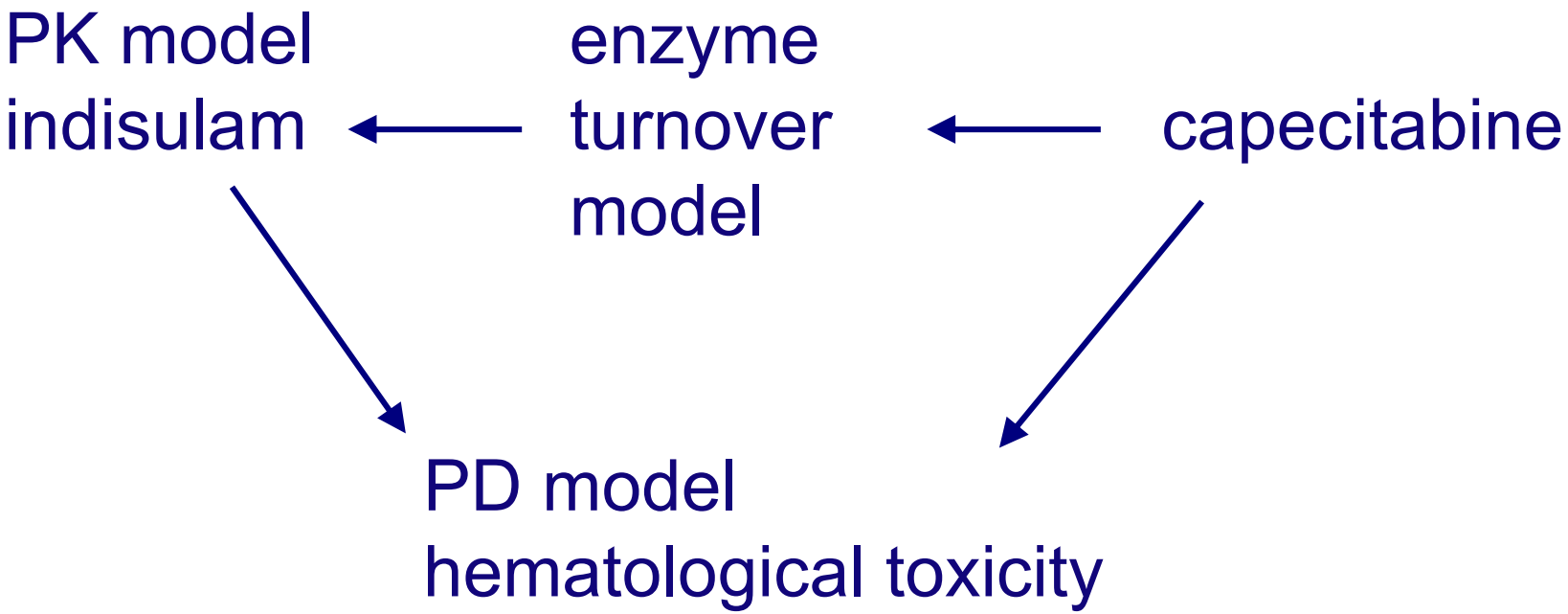
- Major toxicity of indisulam



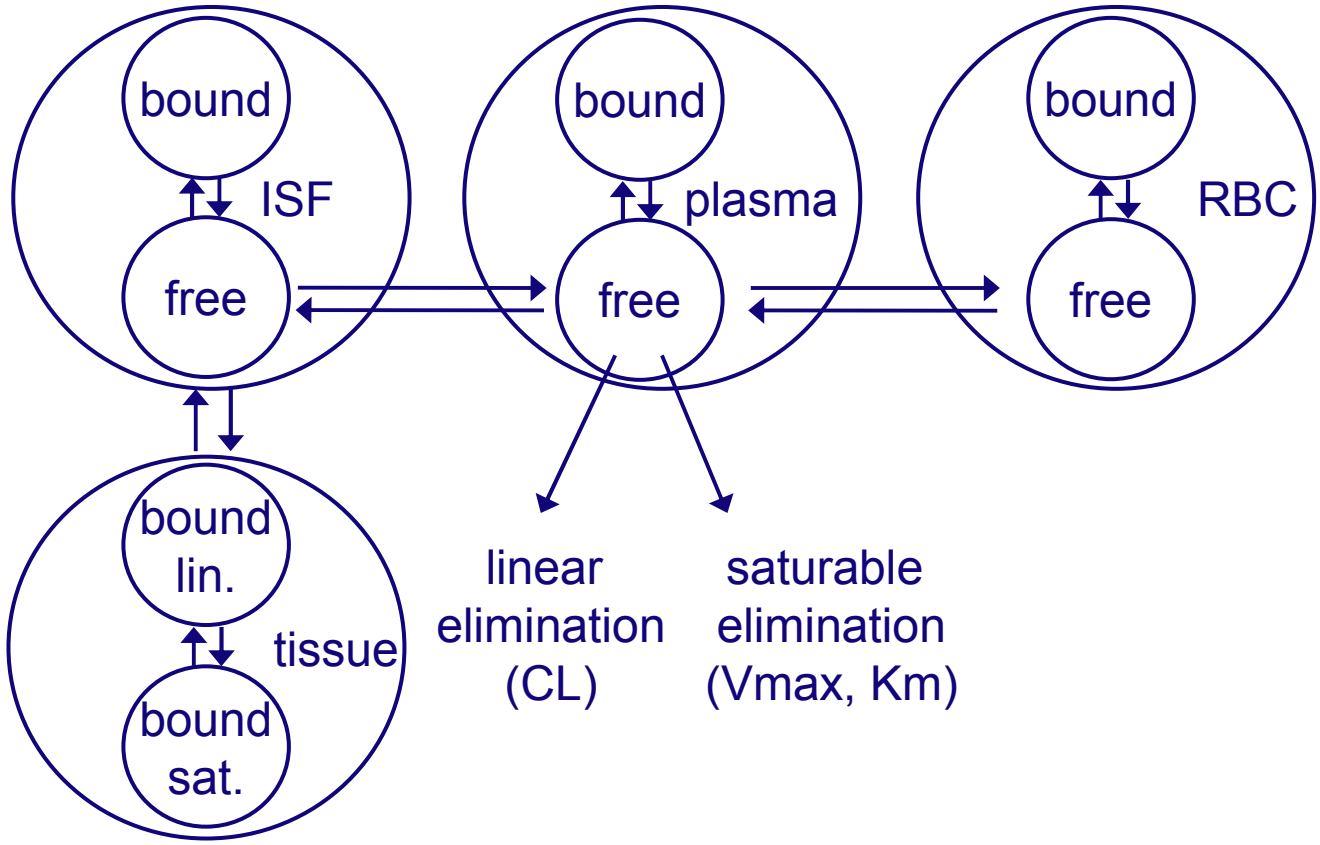
Aims

1) to develop a population PK/PD model for the combination of capecitabine and indisulam
2) to evaluate the role of capecitabine in the induction of hematological toxicity
3) to estimate the impact of a pharmacokinetic interaction on the safety of various dose levels
4) to determine a safe dose of the combination

PK/PD model

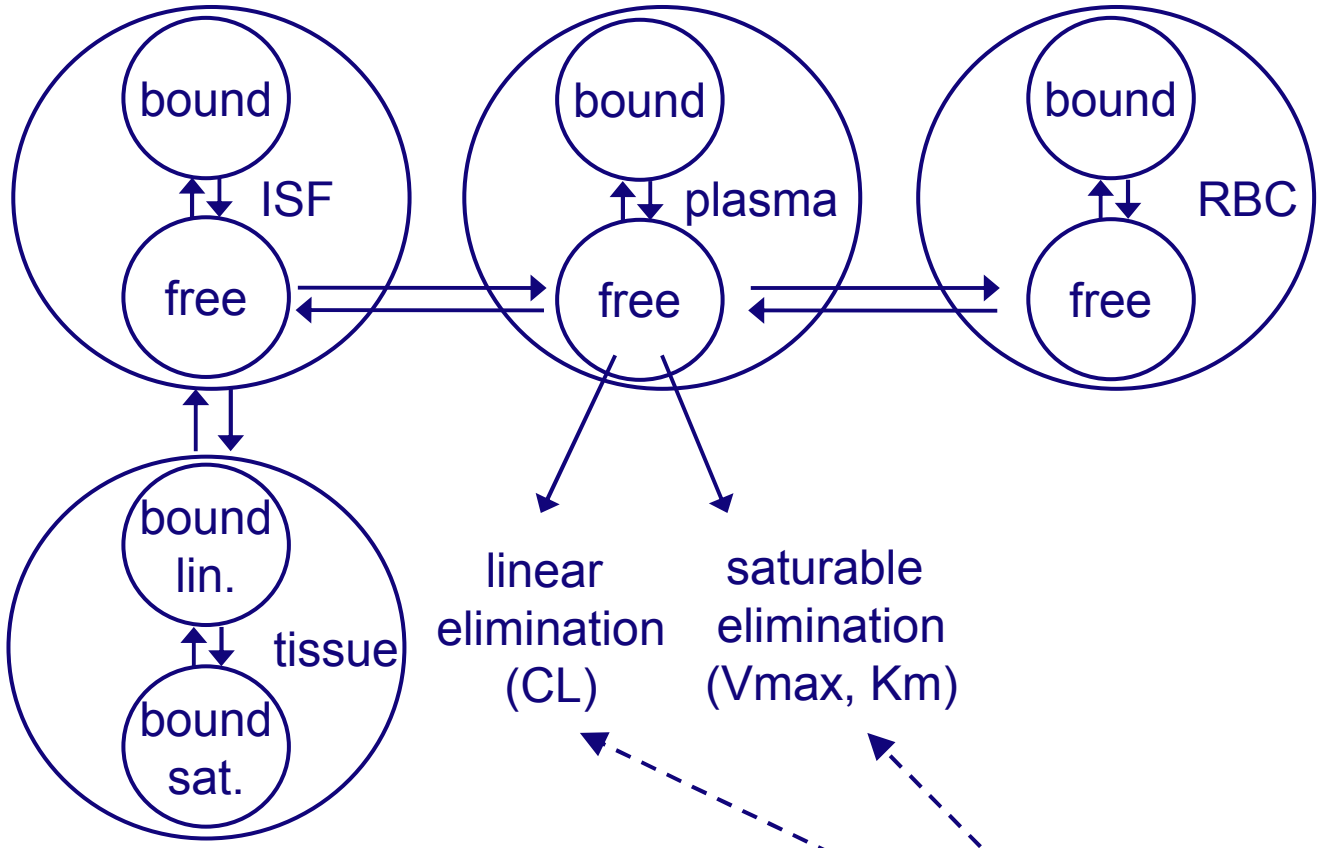

PK model
indisulam
enzyme
turnover
model
capecitabine
PD model
hematological toxicity

PK model indisulam

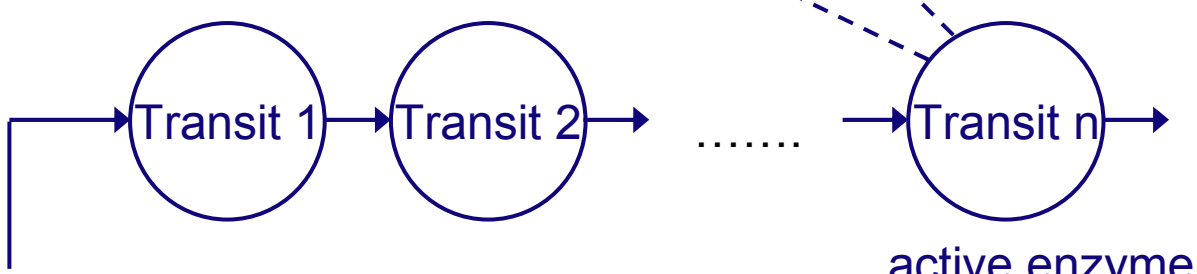


Zandvliet et al. J. Pharmacokin. Pharmacodyn. (in press)

PK model indisulam



enzyme turnover model

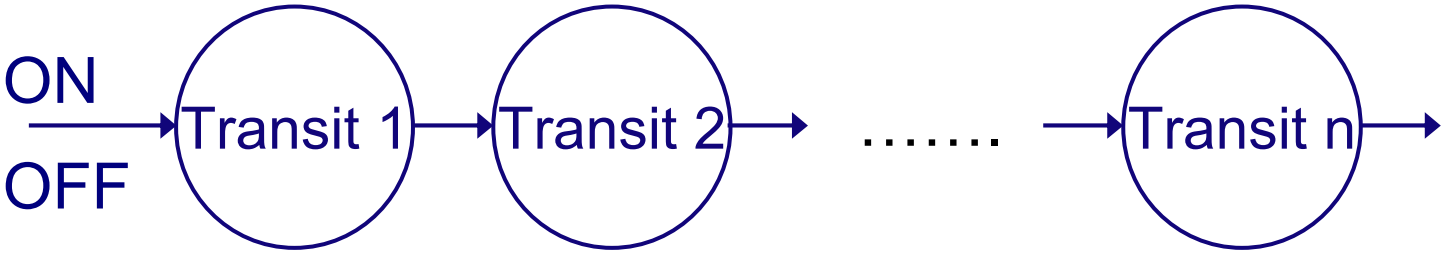


complete inhibition
during capecitabine treatment

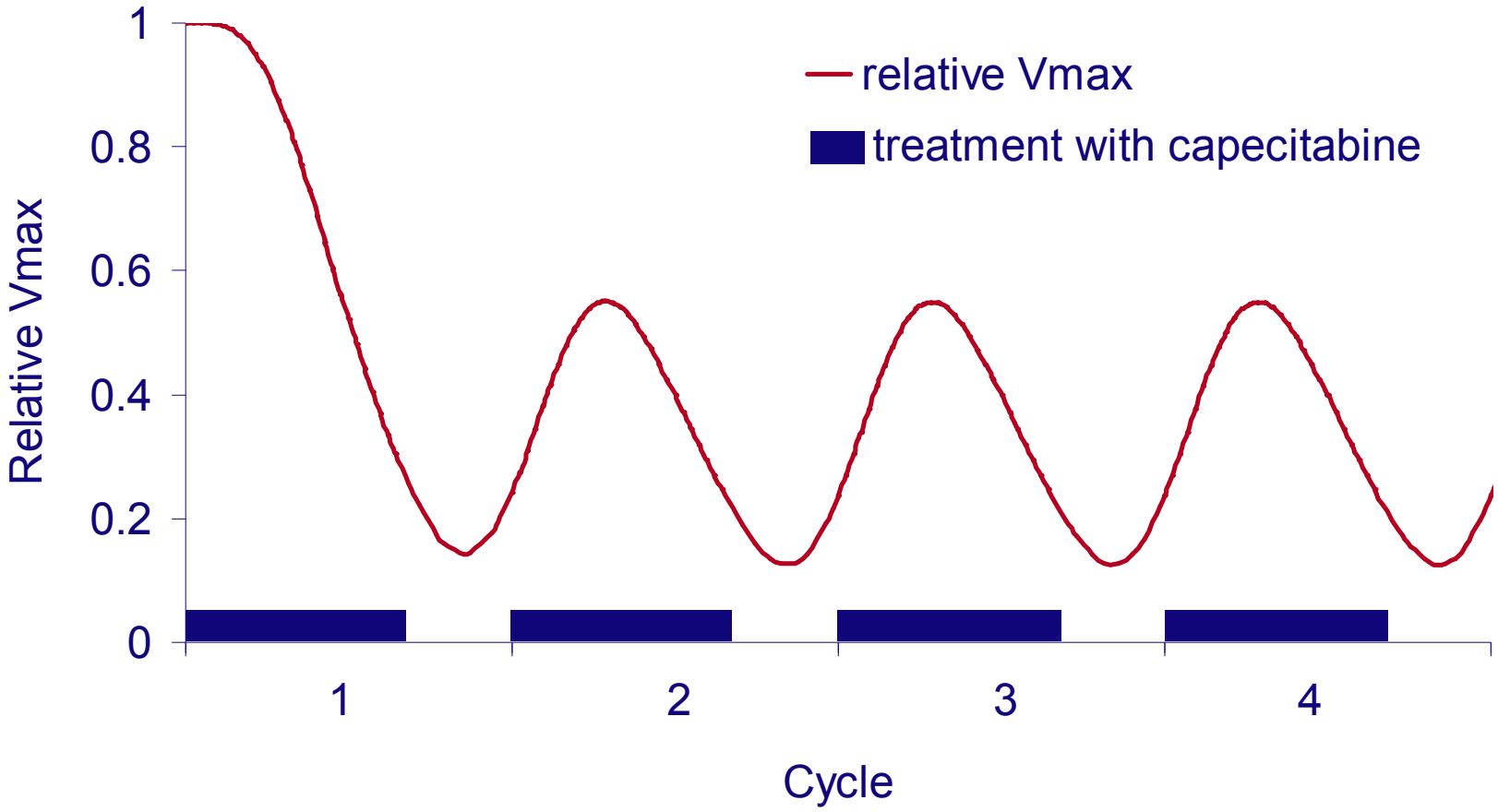
Enzyme turnover model

Capecitabine administration:

Input into first transit compartment:



Time profile of metabolic activity

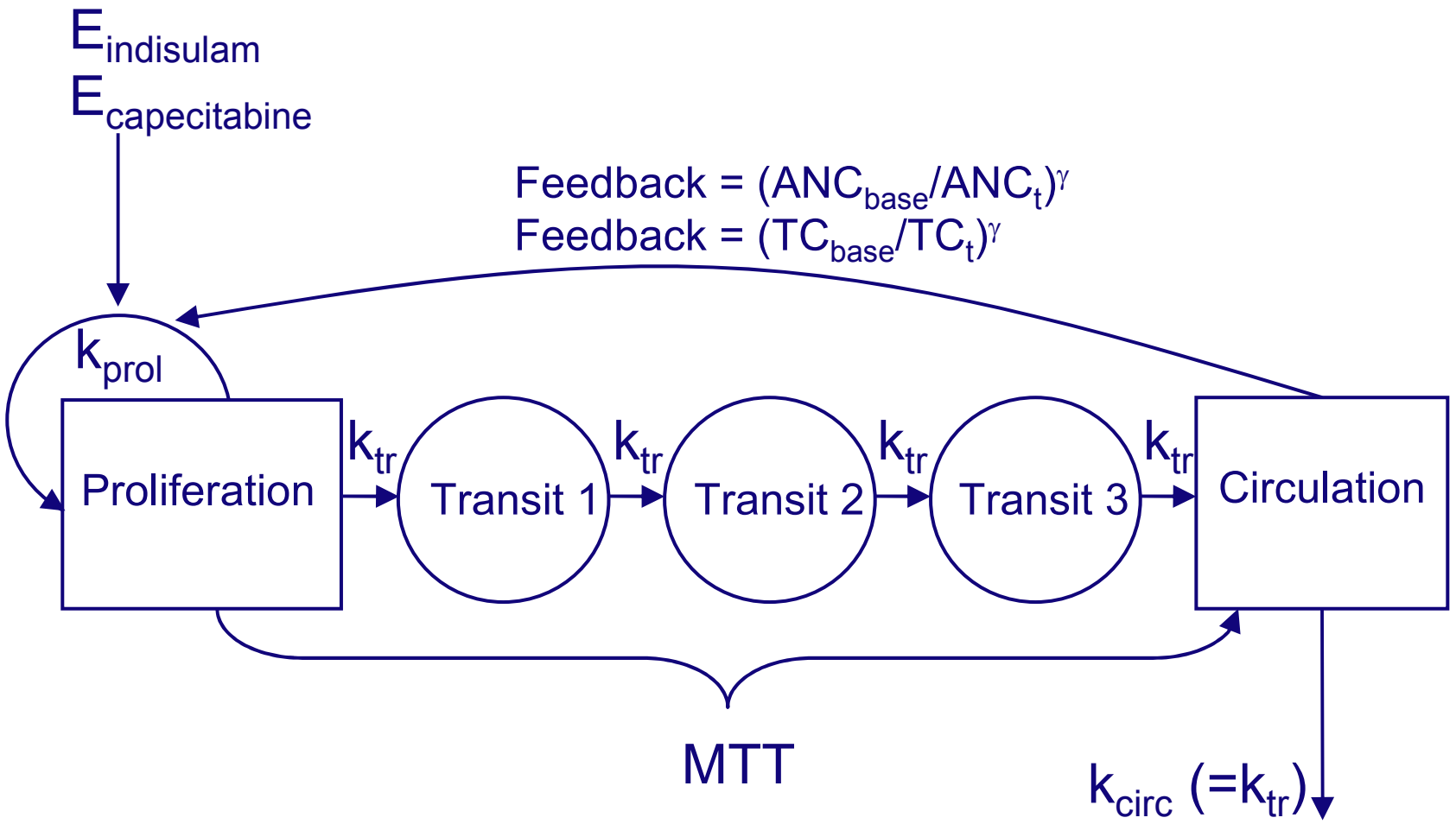


Turnover time = 9.2 days (± 2.1 days)

Indisulam exposure (AUC g*h/L)

dose level (mg/m^2)	Combination therapy	
	First cycle	Subsequent cycles
500	1.2	1.8
550	1.4	2.1
600	1.7	2.5
650	2.0	2.8
700	2.3	3.2

Pharmacodynamic model

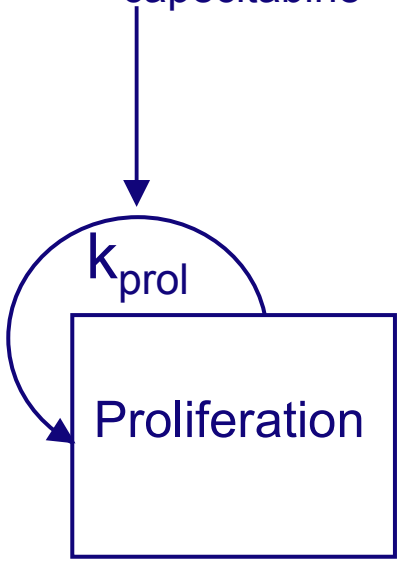


Friberg et al. JCO 2002 ; van Kesteren et al. Invest. New Drugs 2005

Pharmacodynamic model

$E_{indisulam} = slope_{indisulam} \cdot plasma\ concentration$

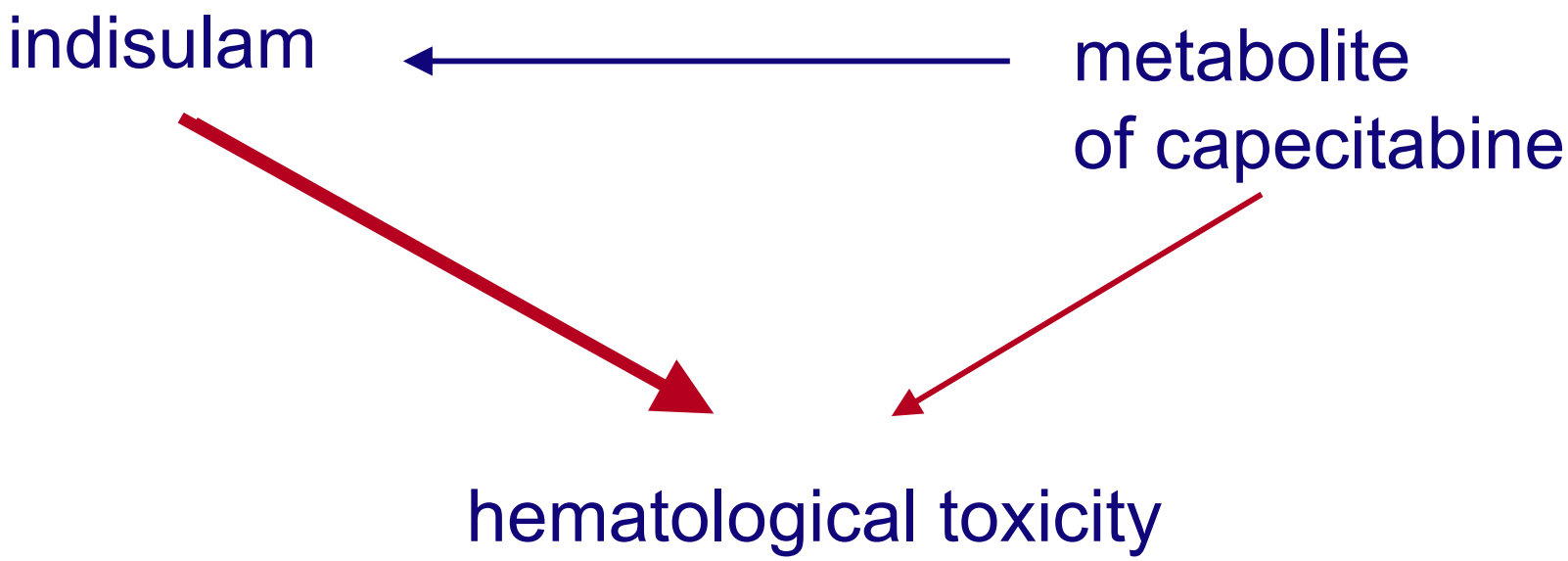
$E_{capecitabine} = slope_{capecitabine} \cdot dose$



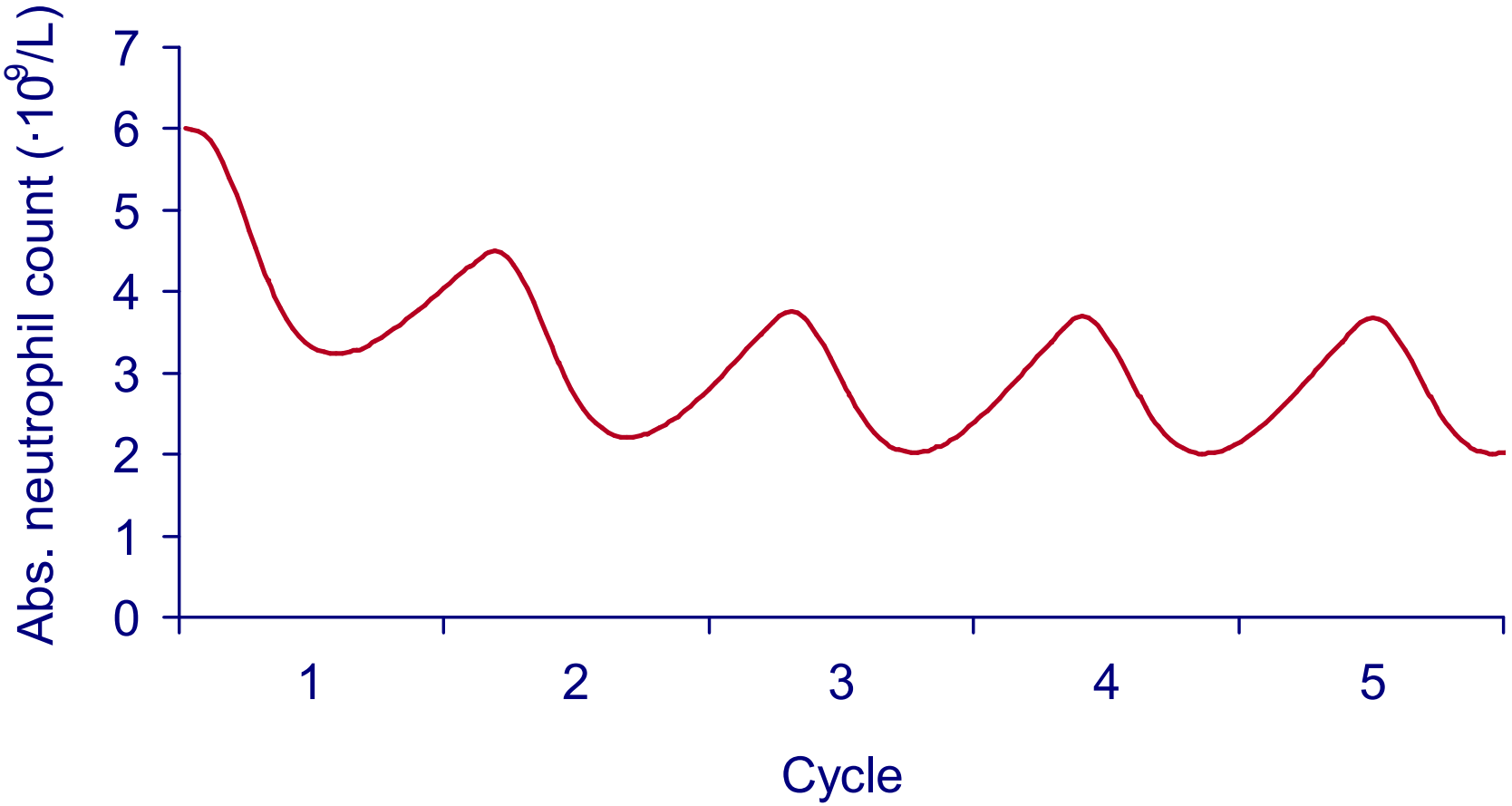
Pharmacodynamic parameters

	Estimate	Interindividual variability
Absolute neutrophil count		
MTT (h)	134	24%
Gamma	0.0834	74%
Slope indisulam (L/mg)	0.0206	39%
Slope capecitabine (mg^{-1})	-	
Proportional residual error (%)	57.5	
Thrombocyte count		
MTT (h)	88.8	19%
Gamma	0.0731	68%
Slope indisulam (L/mg)	0.0113	50%
Slope capecitabine (mg^{-1})	-	
Proportional residual error (%)	58.2	

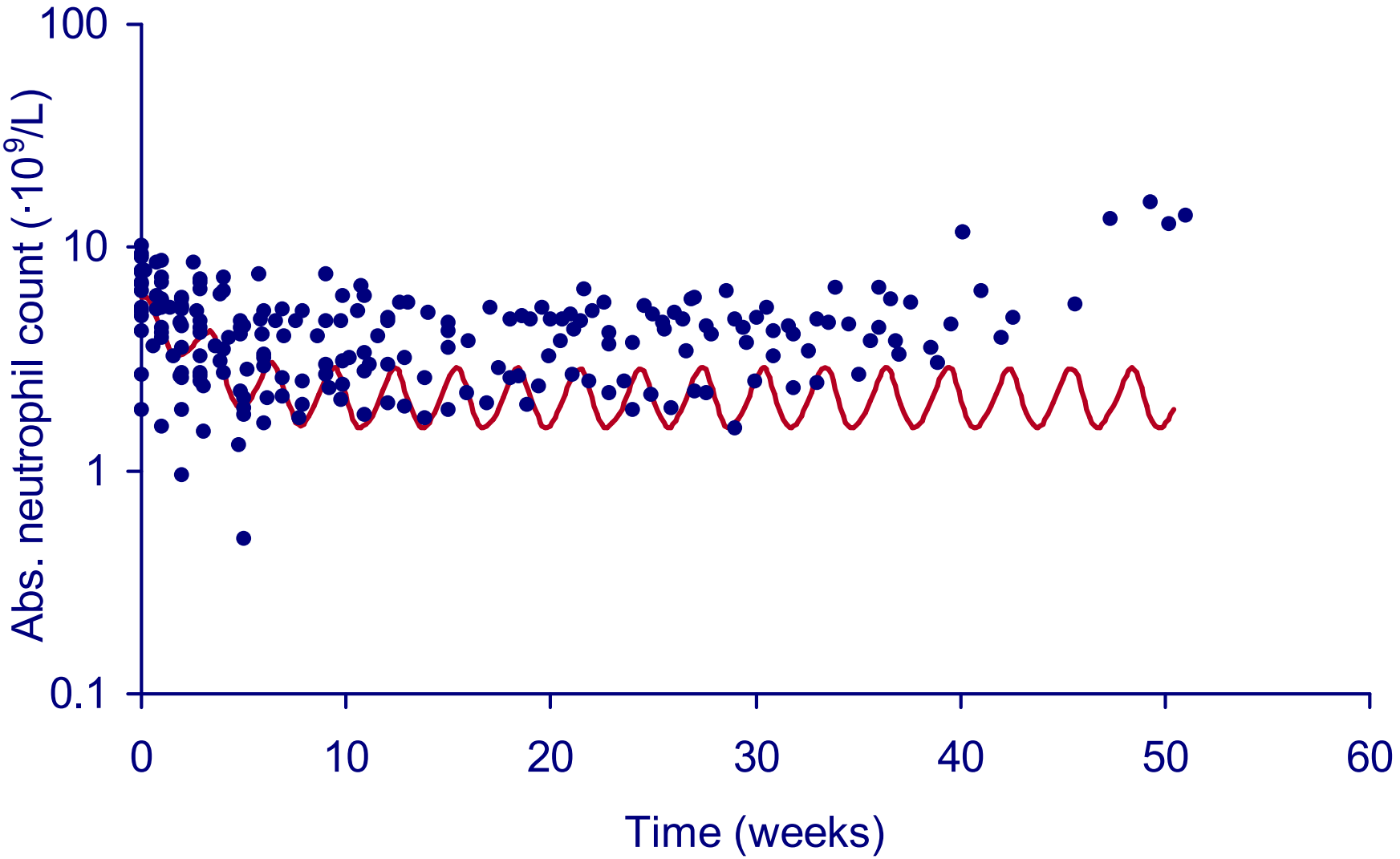
Hematological toxicity



Time profile neutrophil count



Time profile neutrophil count

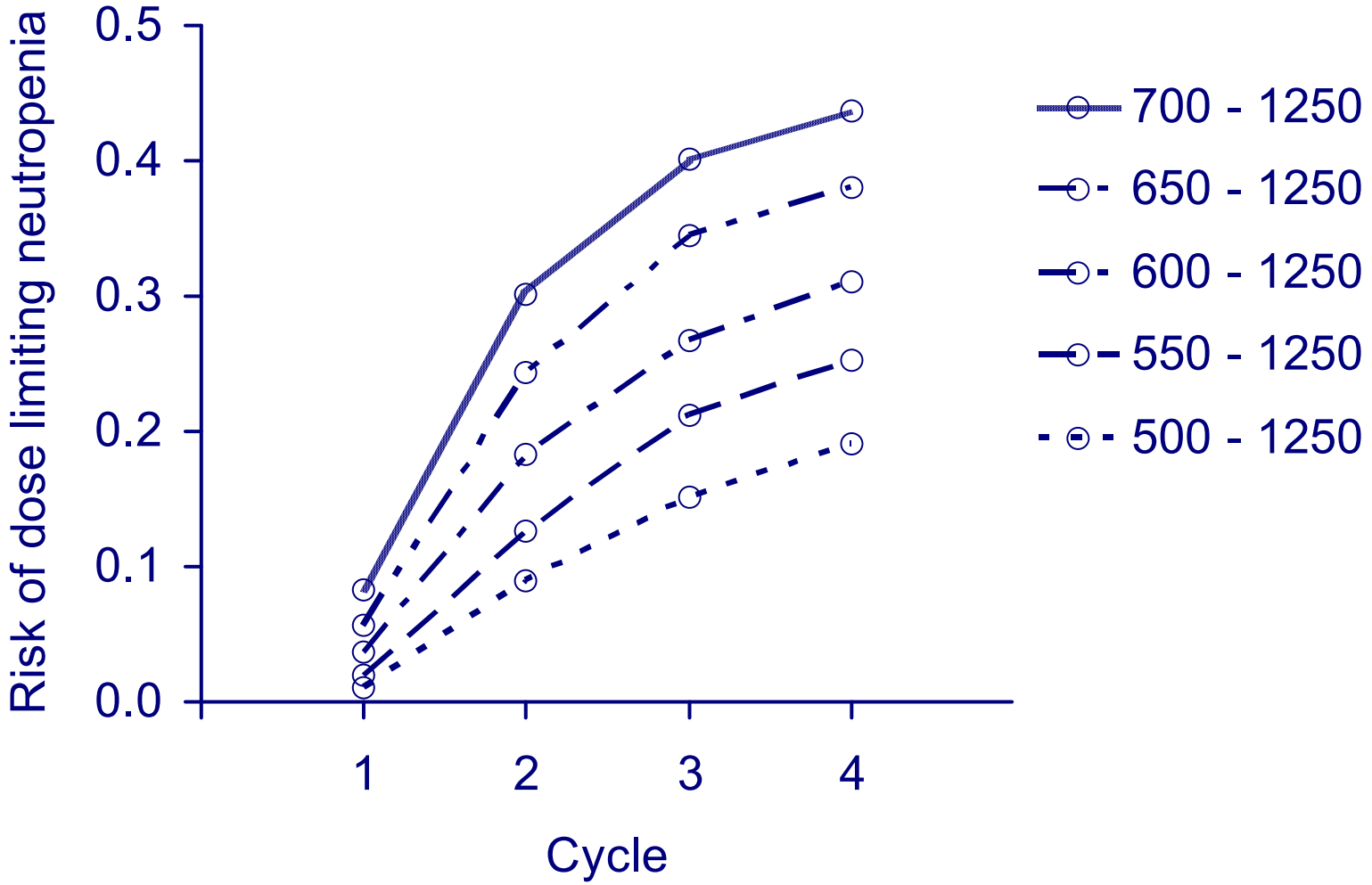


Simulation studies

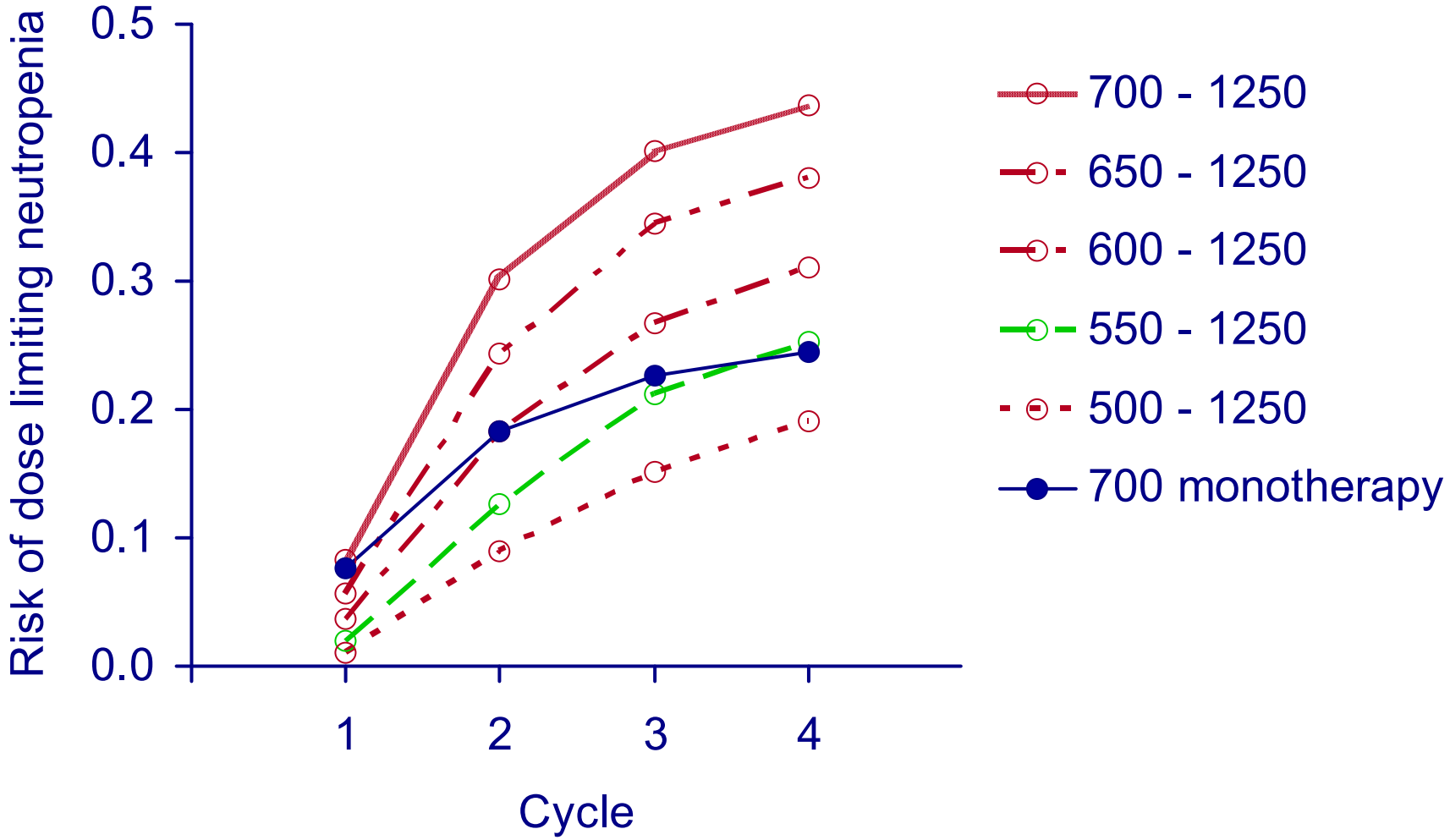
- Risk of dose limiting neutropenia
  - CTC grade 4 neutropenia during >7 days

- Groups of 10,000 patients
  - various doses of indisulam (500-700 mg/m^2)
  - standard dose of capecitabine (1250 mg/m^2 BID)

Risk of dose limiting neutropenia



Risk of dose limiting neutropenia



Conclusions

- co-administration of capecitabine caused a time-dependent inhibition of the saturable elimination pathway of indisulam
- the pharmacokinetic interaction explains the excessive hematological toxicity
- the risk of dose limiting neutropenia is acceptable at a dose level of indisulam 550 mg/m^2 + capecitabine 1250 mg/m^2 BID

Clinical recommendation

- The dose level 500/1250 was safe in a limited number of patients in the clinical study

- This study strongly supports that the dose level 550/1250 is recommended for future studies

Acknowledgment

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