Prospective Bayesian pharmacokinetically guided dosing of cyclophosphamide, thiotepa and carboplatin in high-dose chemotherapy

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INTRODUCTION

Pharmacokinetically guided dosing or
Therapeutic Drug Monitoring:

The use of drug concentration measurements in plasma or other biological fluids to assist in determination of drug dosage for the individual patient

Goal: to provide safe, therapeutic doses in order to improve drug efficacy and reduce toxicity

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INTRODUCTION

Requirements:

- narrow therapeutic index
- substantial interpatient pharmacokinetic variability
- relationship between plasma drug concentration and therapeutic effect or toxicity
- steep relationship between exposure and response
- relatively small intraindividual variability
- available assay for quantification
- available dose adaptation strategy

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INTRODUCTION

High-dose CTC chemotherapy:

- Cyclophosphamide	1500 mg/m^2/day
- Thiotepa	120 mg/m^2/day
- Carboplatin	400 mg/m^2/day or
	AUC=5 mg*min/mg/day

during 4 days

tCTC= 2/3 of total CTC dose

INTRODUCTION

Toxicity in the CTC regimen:

Gastro-intestinal: nausea, vomiting, mucositis, diarrhea
Hemorrhagic cystitis
Veno-occlusive disease of the liver (VOD)
Cardiac toxicity
Sensory neuropathy
Hearing loss
Renal failure
Skin rash

OBJECTIVE

Primary goal:

To investigate whether pharmacokinetically guided dosing of cyclophosphamide, thiotepa and carboplatin reduces the variability in exposure to these compounds

Secondary goal:

To investigate the clinical effect of targeted drug dosing in the CTC regimen

DESCRIBING PHARMACOKINETICS

Population pharmacokinetics:

- data available of 43 patients receiving CTC (65 courses)
- multiple samples during and after CTC
  (approx. 21 samples / course)
- modeled using NONMEM

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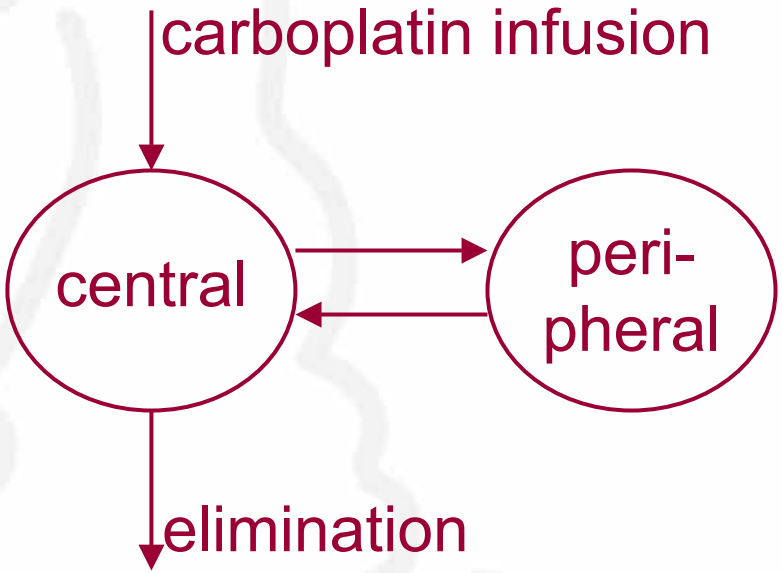
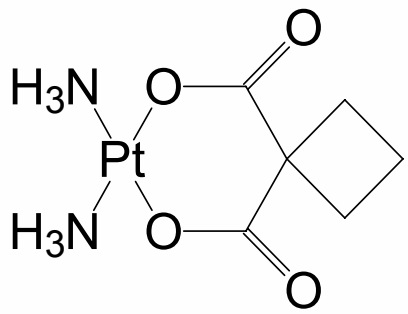
DESCRIBING PHARMACOKINETICS

carboplatin

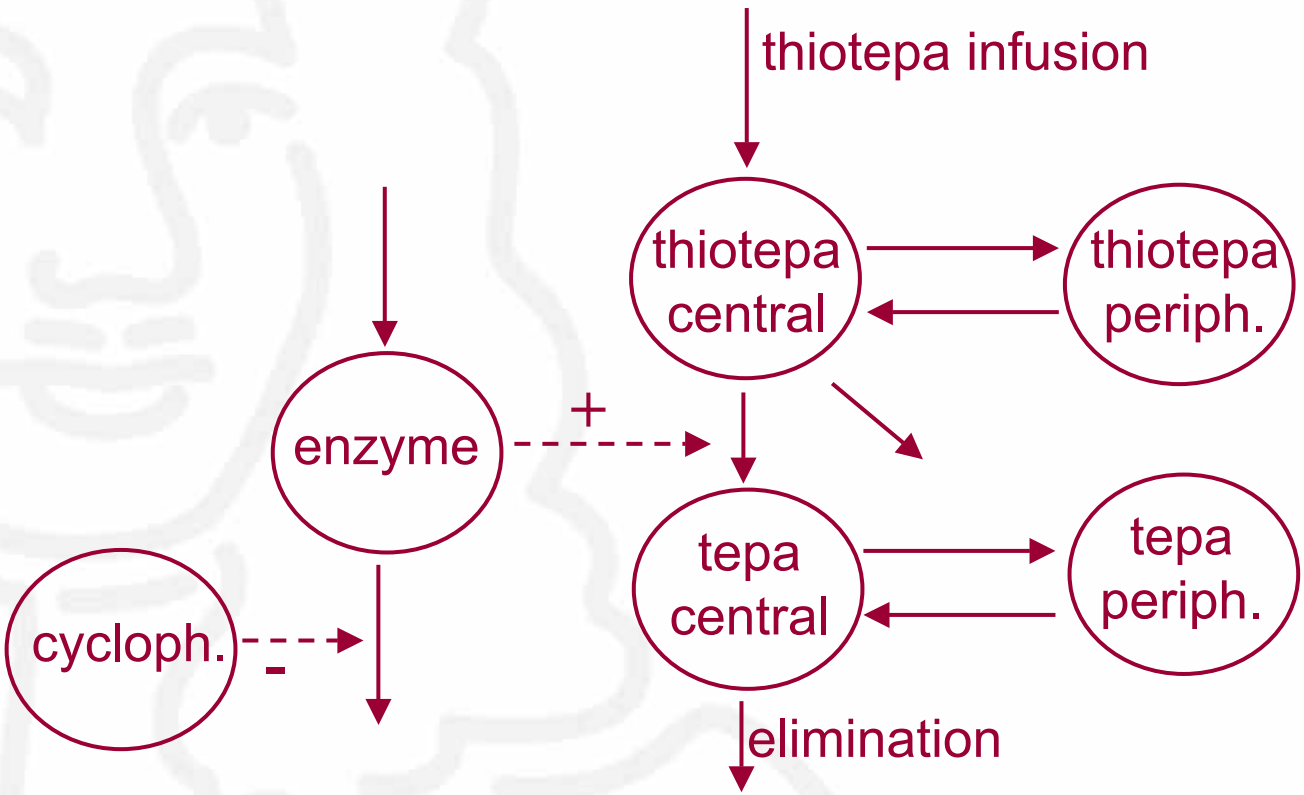


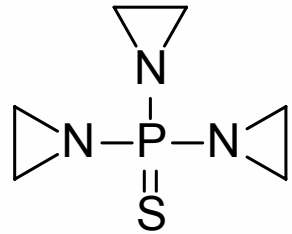


Exposure to carboplatin has been correlated with nephro-, oto- and central nervous system toxicity

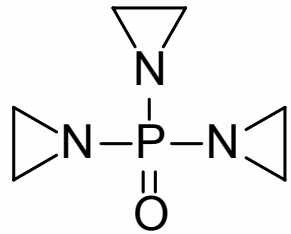
DESCRIBING PHARMACOKINETICS

thiotepa





thiotepa



tepa

Exposure to thiotepa and tepa have been correlated with elevation of transaminases and mucositis

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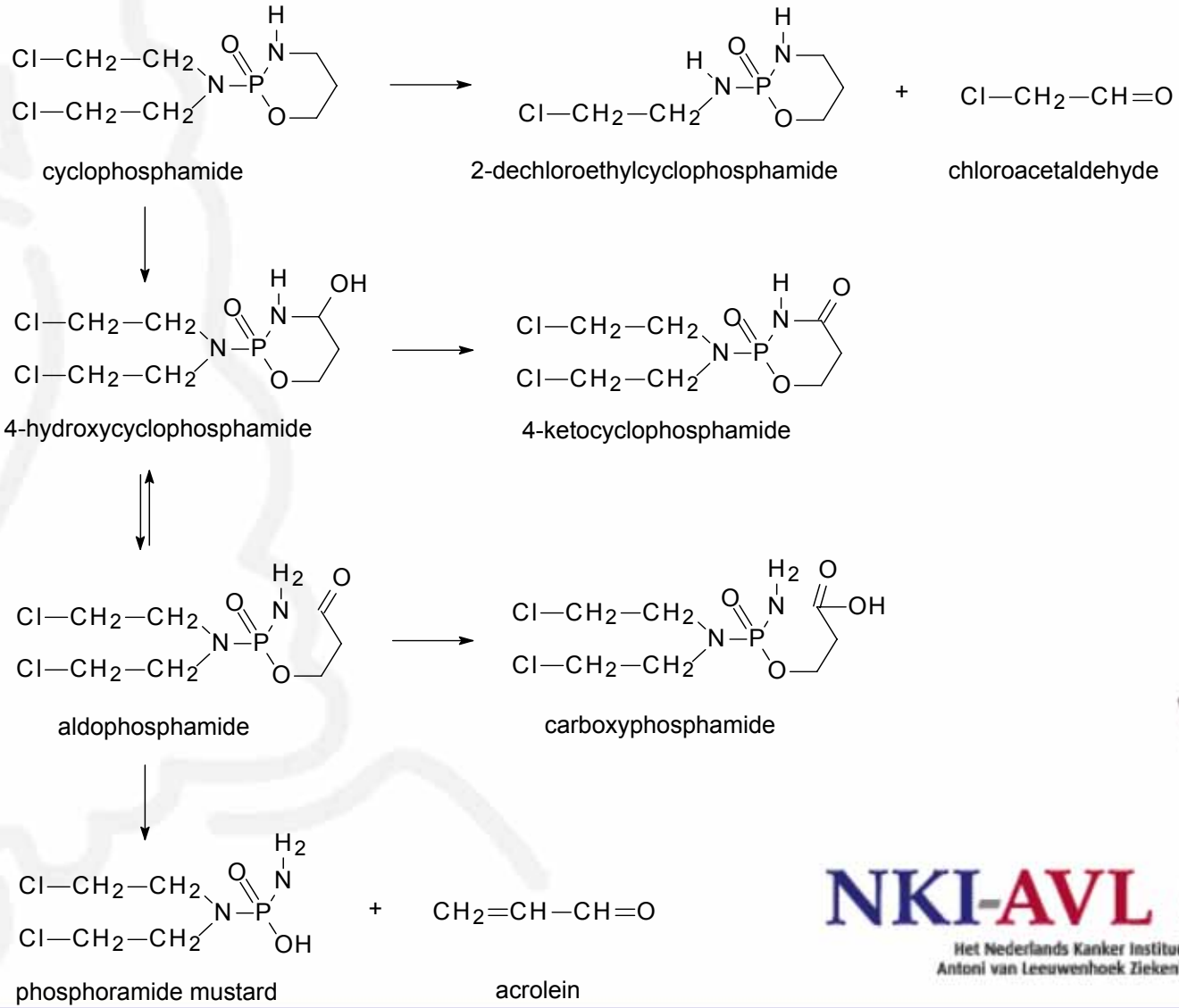
DESCRIBING PHARMACOKINETICS

cyclophosphamide



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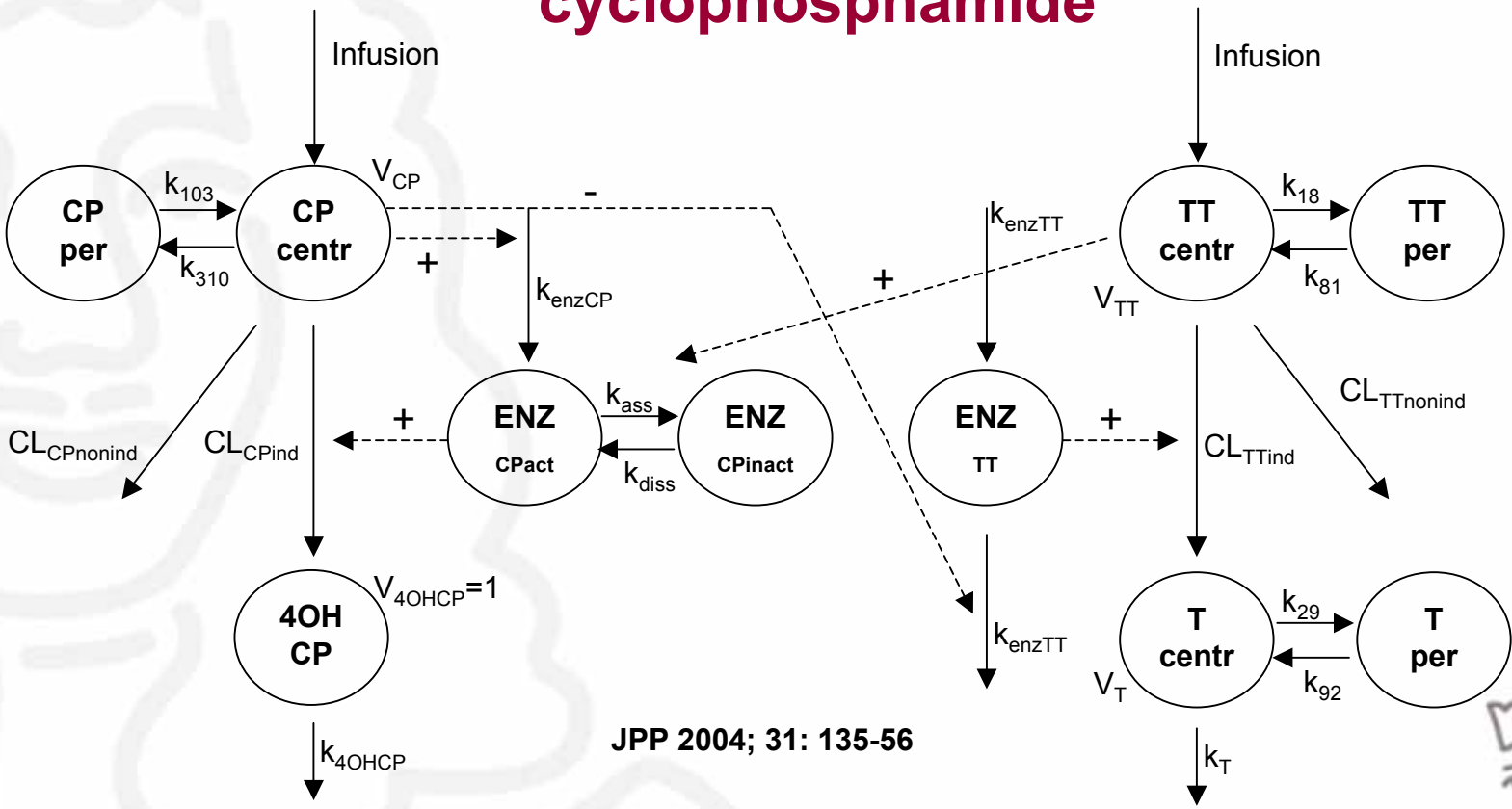
DESCRIBING PHARMACOKINETICS

cyclophosphamide



JPP 2004; 31: 135-56

Exposure to cyclophosphamide has been inversely correlated with cardiotoxicity. Exposure to 4-hydroxy-cyclophosphamide has been correlated with VOD.

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DEFINING SUITABLE TARGET EXPOSURES

Definitive safe and effective target exposure not established

Optimal exposure = median AUC of reference population

	AUC tCTC	AUC CTC
4-hydroxycyclophosphamide	105 µM*h	140 µM*h
thiotepa + tepa	276 µM*h	374 µM*h
carboplatin	13.3 mg*min/ml	20 mg*min/ml

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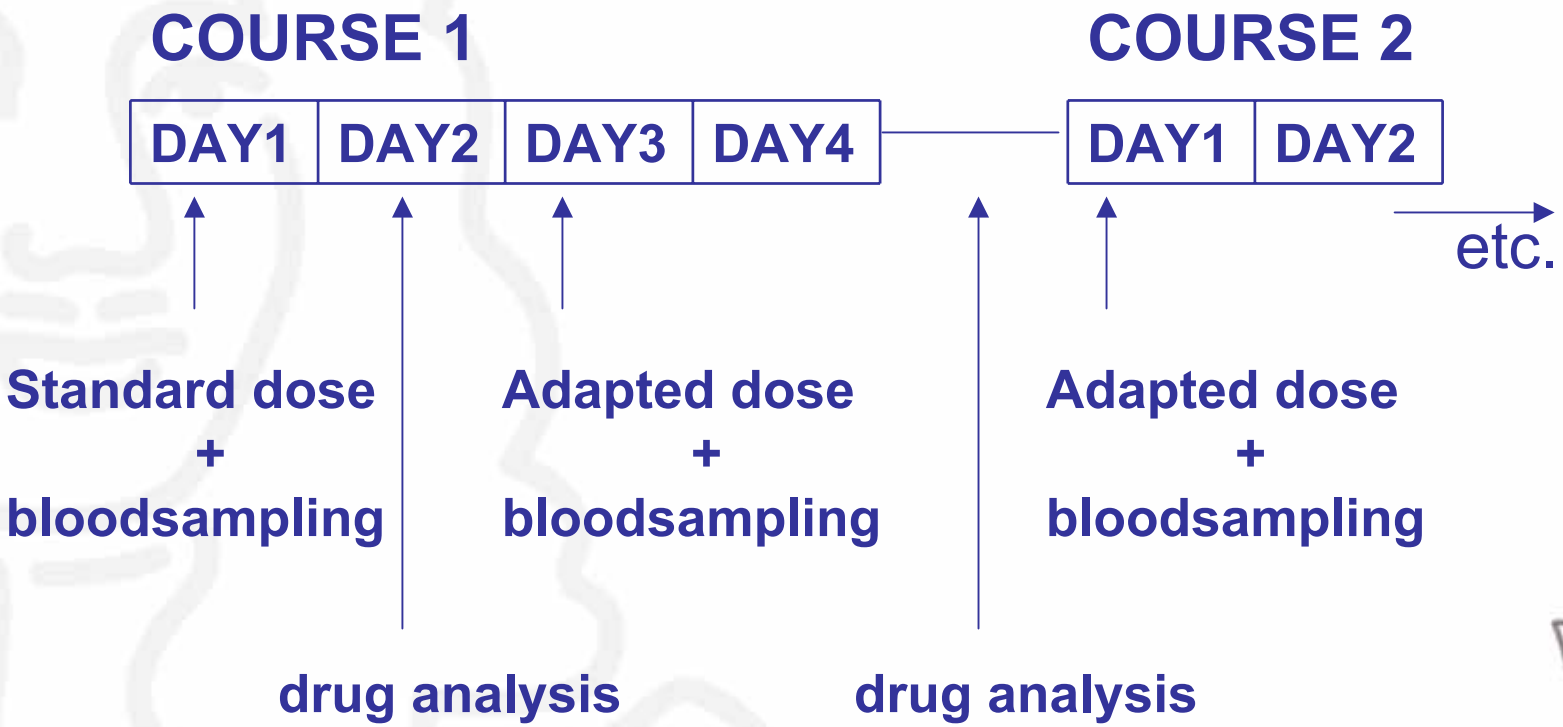
STUDY DESIGN



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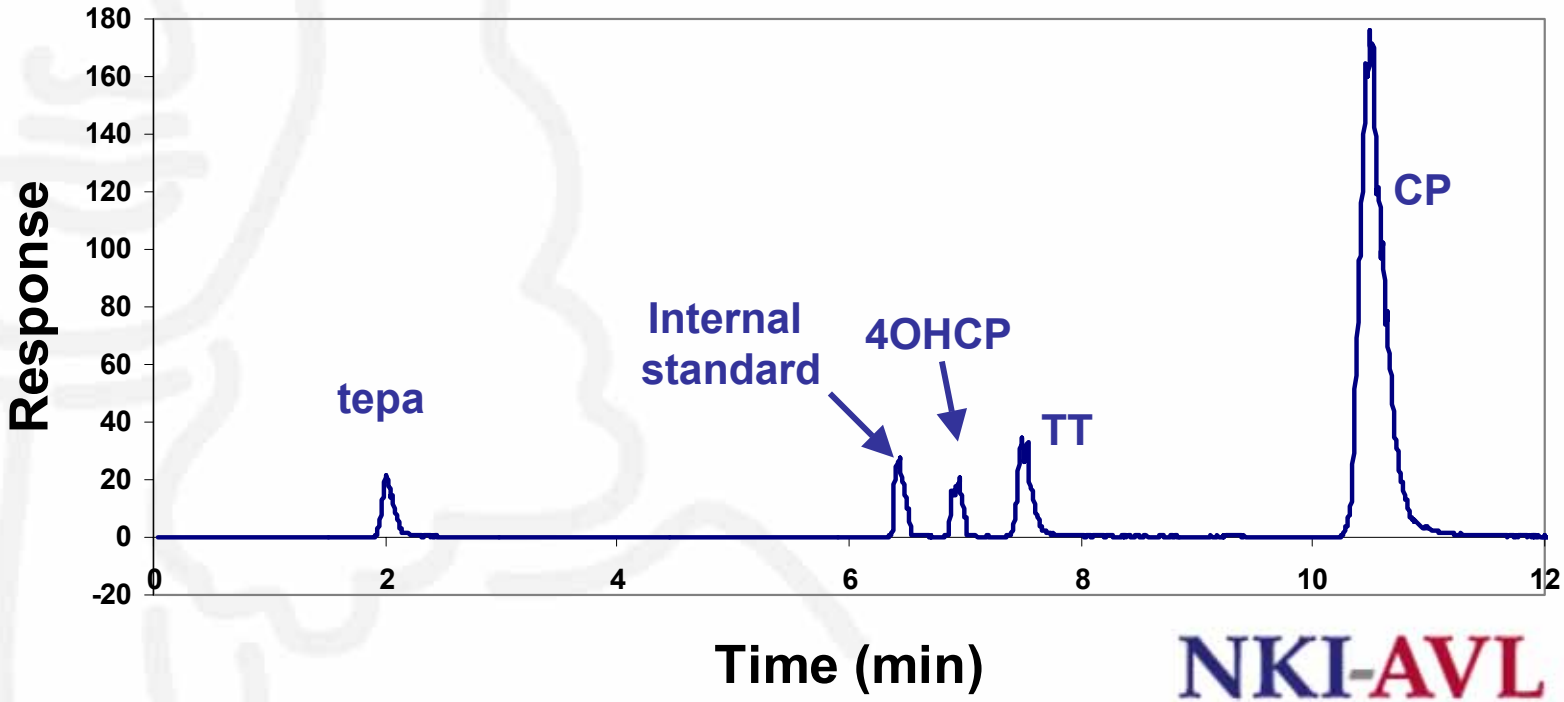
BIOANALYSIS

Simultaneous quantification of cyclophosphamide, 4-hydroxycyclophosphamide, thiotepa and tepa using LC-MS/MS



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RESULTS

Dose adaptations in 46 patients, 108 courses

Number of performed dose adaptations

	Between courses	During courses
Cyclophosphamide	17x	39x
Thiotepa	40x	58x
Carboplatin	43x	65x

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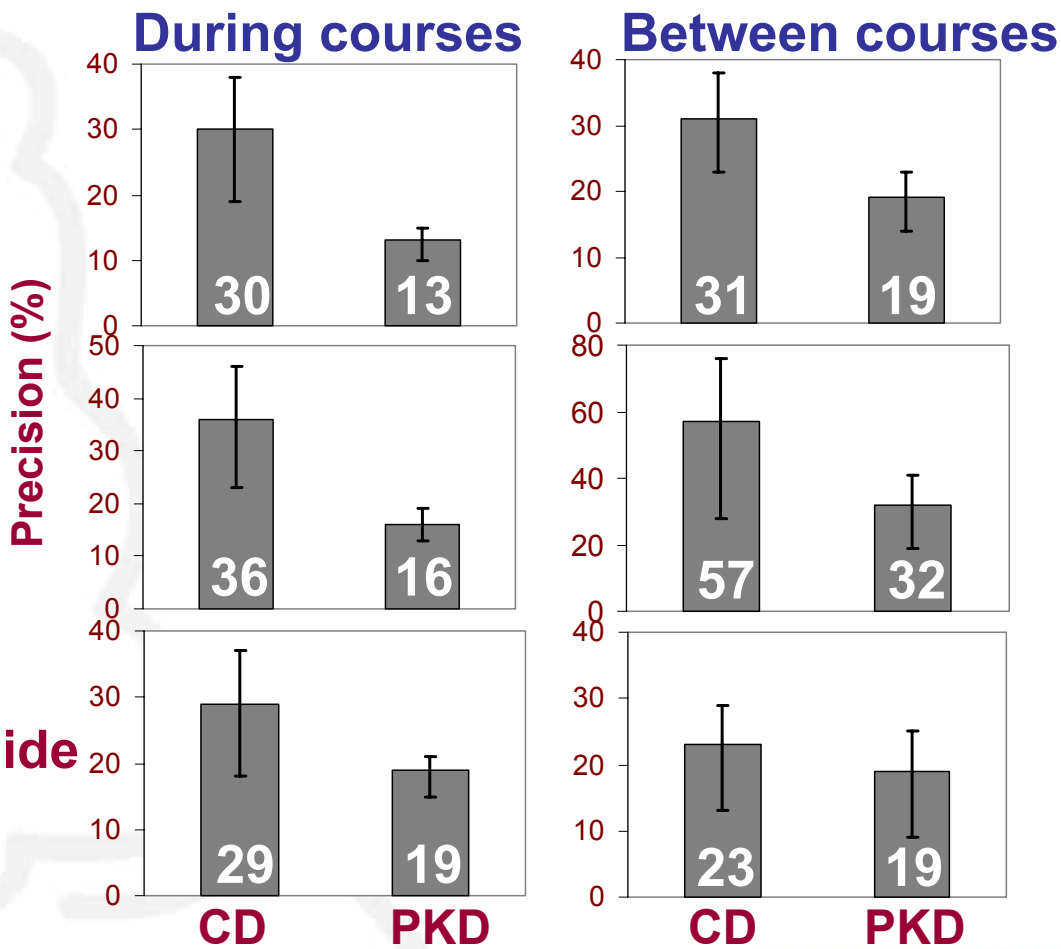
RESULTS



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RESULTS

Adaptations	Exposures within ± 25% of target	
	PKD	CD
Carboplatin		
During courses (n=65)	62 (**95%**)	45 (**69%**)
Between courses (n=43)	35 (**81%**)	27 (**63%**)
Thiotepa		
During courses (n=58)	52 (**90%**)	35 (**60%**)
Between courses (n=40)	28 (**70%**)	25 (**62%**)
Cyclophosphamide		
During courses (n=39)	33 (**85%**)	26 (**67%**)
Between courses (n=17)	13 (**76%**)	13 (**76%**)

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RESULTS

Toxic event	Number of patients	
	Reference patients (n=43)	Patients receiving adapted doses (n=46)
VOD	2 (5%)	3 (7%)[a]
Hemorrhagic cystitis	2 (5%)	3 (7%)
Cardiotoxicity ≥ grade 1	3 (7%)	4 (9%)
Pulmonary toxicity ≥ grade 1	6 (14%)	6 (13%)
Mucositis ≥ grade 3	6 (14%)	5 (11%)
Neuropathy ≥ grade 3	0 (0%)	4 (9%)
Ototoxicity ≥ grade 2	9 (21%)	22 (24%)

[a] none of these patients received an adjusted dose of cyclophosphamide

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CONCLUSIONS

- Pharmacokinetically guided dosing of cyclophosphamide, thiotepa and carboplatin results in reduction of variability in exposures
- Extremely high exposures are effectively prevented
- More patients should be included to draw significant conclusions on the clinical impact of the dosing strategy

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