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Dose individualization of indisulam to reduce the risk of severe myelosuppression

Anthe S. Zandvliet[1], Jan H.M. Schellens[2,3], William Copalu[4], Jantien Wanders[4], Jos H. Beijnen[1,2], Alwin D.R. Huitema[1]

(1) Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute/Slotervaart Hospital, Amsterdam, The Netherlands;
(2) Beta Faculty, Department of Pharmaceutical Sciences, Division of Biomedical Analysis, Section of Drug Toxicology, Utrecht University, Utrecht, The Netherlands;
(3) Department of Clinical Pharmacology, Division of Medical Oncology, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands;
(4) Eisai Ltd., London, United Kingdom.

Introduction

Indisulam:
- An investigational anticancer drug.
- Currently in phase II clinical development.
- Myelosuppression is dose-limiting.
- Treatment with indisulam is complicated by wide interpatient variability regarding drug exposure and severity of myelosuppression.

Aim:
- To investigate the impact of patient-related covariates on PK-PD parameters related to indisulam-induced hematological toxicity.
- To identify patients at risk of developing severe myelosuppression.
- To develop an algorithm for dose individualization of indisulam.

Methods

Data:
- 7 phase I studies and 6 phase II studies.
- 412 patients.

PK-PD model:
- Previously developed structural model (Fig1).
- Indisulam concentrations, neutrophil and thrombocyte counts simultaneously analyzed.

Covariate analysis :
- Covariate analysis according to a pre-specified plan: only plausible relationships were evaluated.
- Demographics, physical condition, prior treatment, concomitant medication, CYP2C genotype and biochemistry.

Evaluation of clinical relevance :
- Simulation study to determine the relative risk of dose limiting myelosuppression for the 2.5 and 97.5 percentiles of each patient characteristic versus the median.
- A relative risk of less than 0.9 or more than 1.1 was considered clinically relevant.

Development of a dosing algorithm :
- The correlation between patient characteristics and the risk of severe neutropenia was minimized.

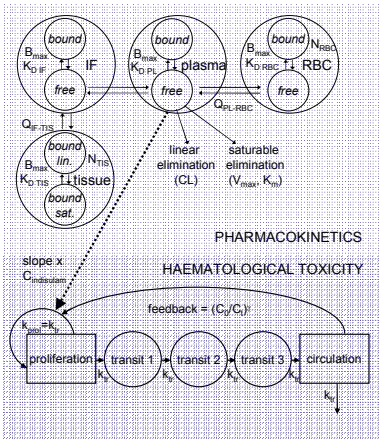

Figure 1: Structural PK-PD model of indisulam-induced myelosuppression.[1-3]

Results

Table 1: Statistically significant covariate relationships and their clinical relevance.

Pharmacokinetic covariates	Related parameter	Covariate effect	Relative risk (RR) of dose limiting haematological toxicity
body surface area (m^2) and **WT** (kg)	V_{max} CL $B_{max\ TIS}$	$(BSA/1.78)^{1.20}$ $(WT/69)^{0.75}$ $(WT/69)^{-0.621}$	BSA=1.42 / WT = 45→ RR= 1.13
race *(0=Japanese, 1=Caucasian/Hispanic/Black)*	V_{max}	$(1+0.613)^{race}$	Japanese → RR= 1.19
CYP2C9 *3 polymorphism *(wildtype: MUT=0; heterozygous: MUT=1; homozygous: MUT=2)*	V_{max}	(1-0.309·MUT)	heterozygous → RR= 1.15 homozygous→ RR= 1.38
CYP2C19 *2 / *3 polymorphism *(wildtype: MUT=0; heterozygous: MUT=1; homozygous: MUT=2)*	CL	(1-0.487·MUT)	heterozygous → RR= 1.45 homozygous→ RR= 2.34
Pharmacodynamic covariates			
sex *(0=female; 1=male)*	MTT_{neu} MTT_{plt}	$(1+0.225)^{sex}$ $(1+0.214)^{sex}$	female → RR= 1.18
prior chemotherapy *(no prior chemotherapy: PC=0; one or two prior courses: PC=1; three or more prior courses: PC=2)*	$slope_{neu}$	(1+PC·0.0994)	PC=2 → RR= 1.06

Table 2: Algorithm for dose individualization.

Patient characteristic	Score	Example 1	Example 2
Sex			
Female	-3		-3
Male	0	0	
CYP2C genotype			
wildtype	0	0	
heterozygous CYP2C9*3	-2		
homozygous CYP2C9*3	-4		
heterozygous CYP2C19*2 or *3	-6		
homozygous CYP2C19*2 or *3	-12		-12
Race			
Caucasian	0	0	
Japanese	-1		-1
Baseline neutrophil count			
< $4 \cdot 10^9$/L	-5		
> $8 \cdot 10^9$/L	+5	+5	
Total score		+5	-16
Individual dose (mg/m²)	775 + total score·25	900	375

Example 1: application of the dosing algorithm for a Caucasian male patient with a wildtype genotype and a high baseline neutrophil count of $9 \cdot 10^9$/L → **900 mg/m²**.
Example 2: application of the dosing algorithm for a Japanese female patient with a CYP2C19 *2/*2 genotype and a normal baseline neutrophil count → **375 mg/m²**.

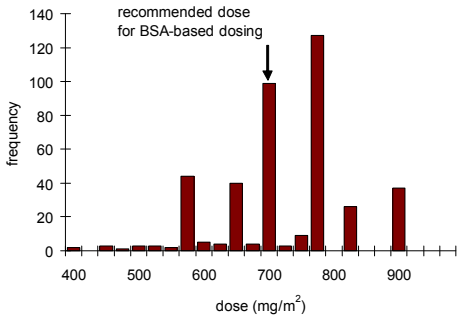

Figure 2: Distribution of individual indisulam doses based on the dosing algorithm, for each of the 412 patients in the study population .

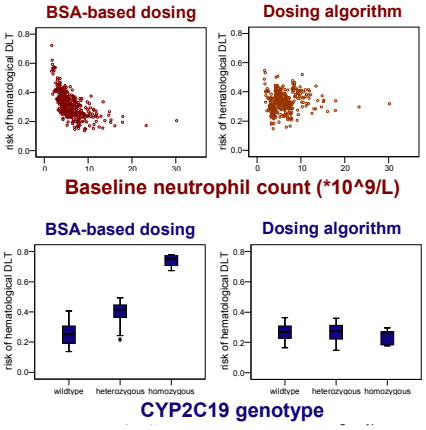

Figure 3: Risk of severe myelosuppression after a 1-hour infusion of indisulam.

- Body size, CYP2C genotype and baseline blood cell counts were the major determinants of the risk of dose-limiting haematological toxicity.
- A reduced dose was recommended for 1 out of every 4 patients in order to enhance treatment safety.
- An increased dose was recommended for 2 out of every 4 patients, which may be beneficial for treatment efficacy.

Conclusion

- This study has identified patient characteristics related to an increased risk of severe myelosuppression after therapy with indisulam.
- Dose individualization based on these patient characteristics may contribute to treatment optimization.

References

[1] Zandvliet et al. JPP 2006
[2] Friberg et al. JCO 2002
[3] Van Kesteren et al. Invest New Drugs 2005