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Pharmacogenetically guided dosing of the anticancer agent indisulam normalizes the risk of severe hematological toxicity

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Introduction

The anticancer agent indisulam is metabolized by the cytochrome P450 enzymes CYP2C9 and CYP2C19. Polymorphisms of these enzymes may affect the elimination rate of indisulam. Consequently, variant genotypes may be clinically relevant predictors for the risk of developing severe hematological toxicity.

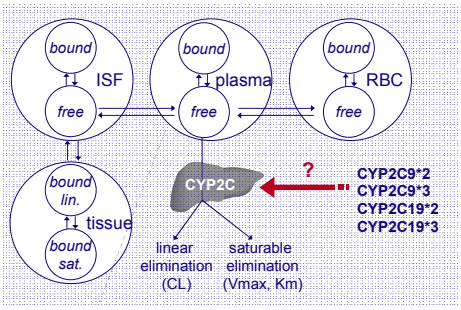

Figure 1. Pharmacokinetic model of indisulam [1]

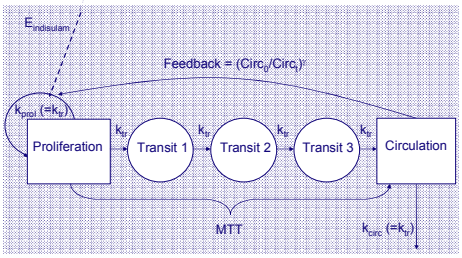

Figure 2. Pharmacodynamic model of chemotherapy-induced hematological toxicity [2]

Objectives

- to evaluate the effect of genetic variants of CYP2C9 and CYP2C19 on the pharmacokinetics of indisulam,
- to determine the relative risk of dose limiting neutropenia,
- to develop a pharmacogenetically guided dosing strategy.

Methods

1. Pharmacogenetics

Pharmacogenetic screening of CYP2C polymorphisms was performed in 67 Caucasian and Japanese patients treated with indisulam. The relationships between allelic variants of CYP2C genes and the elimination pharmacokinetic parameters (CL, Vmax, Km) were verified in a multivariate analysis using NONMEM.

2. Risk of dose limiting neutropenia

Dose limiting neutropenia: CTC grade 4 neutropenia (absolute neutrophil count <0.5*10^9/L) during at least seven days. Populations of 10,000 patients with variant genotypes were simulated to receive the recommended indisulam dosage of 700 mg/m^2. For each genotype, the proportion of patients who experienced dose limiting neutropenia was assessed.

3. *Pharmacogenetically guided dosing strategy*

A dosing strategy was developed by reiteration of the simulation study using various reduced dosage regimens for patients with one or more high risk mutations. Normalization of the relative risk of neutropenia was verified.

Results

1. Pharmacogenetics

Table 1. Genotype frequencies in the study population.

	CYP2C9*2	CYP2C9*3	CYP2C19*2	CYP2C19*3
Caucasian				
Wild-type	35	36	37	46
Heterozyg.	10	9	9	0
Homozyg.	1	1	0	0
Japanese				
Wild-type	21	19	10	18
Heterozyg.	0	2	7	3
Homozyg.	0	0	4	0

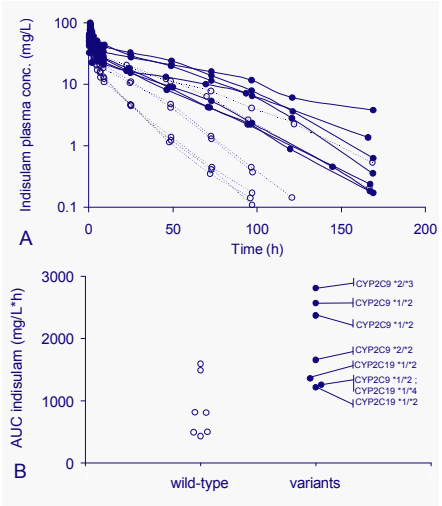

Figure 3. Plasma concentrations (A) and AUC values (B) of patients with a wild-type (○) or variant (●) genotype after treatment with 500 mg/m^2 indisulam.

Table 2. Effect of heterozygous mutations.

polymorphism	effect	effect size	95% CI [1]	P-value
CYP2C9*2	insignificant			
CYP2C9*3	Vmax	27%	13%-40%	<0.0001
CYP2C19*2 CYP2C19*3	CL	38%	31%-45%	<0.0001

[1] The 95% confidence interval was established by likelihood profiling.

2. Risk of dose limiting neutropenia

The risk of severe neutropenia was significantly increased for patients with CYP2C9*3, CYP2C19*2 and CYP2C19*3 mutations.

Table 3. Simulated relative risk of dose limiting neutropenia after administration of 700mg/m^2 indisulam.

	CYP2C9*3 Heterozyg.	CYP2C9*3 Homozyg	CYP2C19*2 CYP2C19*3 Heterozyg.	CYP2C19*2 CYP2C19*3 Homozyg.
Caucasian	1.45 (1.20-1.77)	2.24 (1.48-3.33)	1.96 (1.73-2.19)	NA
Japanese	1.56 (1.11-1.58)	NA	2.04 (1.74-2.37)	4.43 (3.28-6.01)

NA = not applicable.

3. *Pharmacogenetically guided dosing strategy*

The recommended starting dose of indisulam was 700 mg/m^2 in patients with a wild-type genotype. For each CYP2C9*3 allele, a dose reduction of 50 mg/m^2 was required. For each *2 or *3 mutation in the CYP2C19 gene, the recommended dose was reduced by 100 mg/m^2. This strategy for dose adaptation resulted in normalization of the risk of severe neutropenia (relative risk 0.99-1.36) in patients with CYP2C polymorphisms.

Conclusions

1. CYP2C9*3, CYP2C19*2 and CYP2C19*3 polymorphisms resulted in a reduced elimination rate of indisulam.
2. Patients with one or more of these CYP2C mutations have a higher risk of developing severe side effects.
3. Screening for CYP2C polymorphisms before treatment with indisulam is recommended. The initial indisulam dosage should be reduced in patients with high risk mutations.

References

[1] Zandvliet AS et al. *J Pharmacokin Pharmacodyn.* (in press)

[2] van Kesteren C et al. *Invest New Drugs* 2005; 23(3):225-234.