A latent-variable model for Sorafenib-induced HFS in cancer non-selected patients to predict toxicity kinetics

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Introduction

- **Sorafenib** is a multi-kinase inhibitor, targeting especially Raf-ERK and VEGFR pathways, approved for the treatment of advanced renal cell and hepatocellular carcinoma; it induces cutaneous, haematological and metabolic toxicities.
- **Hand-Foot Syndrome** (HFS) is characterized by an inflammation of the skin on palms and soles. Its pathophysiological mechanism has not been fully understood yet, but several hypotheses suggested the accumulation of a toxic compound in skin cells. Severe HFS episodes can lead to treatment discontinuation.

Objectives

- **Propose a physiologically coherent model for the sorafenib-induced HFS on a long-term basis**
- **Quantify the HFS risk dynamics, linked to the exposure to sorafenib**
- **Evaluate by simulation the dynamics of sorafenib-induced HFS under different administration regimen**

Patients & Methods

Patients

- 89 non-selected patients with HCC, RCC, melanoma, sarcoma or thyroid cancer, treated with sorafenib
- Treatment duration, sorafenib regimen, number and frequency of HFS observations were highly variable between patients

Model

- Non-linear mixed effect model, so called “population approach” to link sorafenib administration and the risk of each HFS score
- Sorafenib PK described by Hornecker et al [1]: one-compartment model with first-order elimination and saturable absorption (due to intestinal loss)
- Accumulated sorafenib impacted on the kinetics of a latent variable (LV, interpretable as a non-identified biomarker) [2]. Probabilities for each HFS score (0, 1, 2, 3) were computed from a probit function of LV and thresholds (γ)
- Parameters were estimated using NONMEM7.1.2
- Model evaluation was driven by goodness-of-fit and simulation-based diagnostics

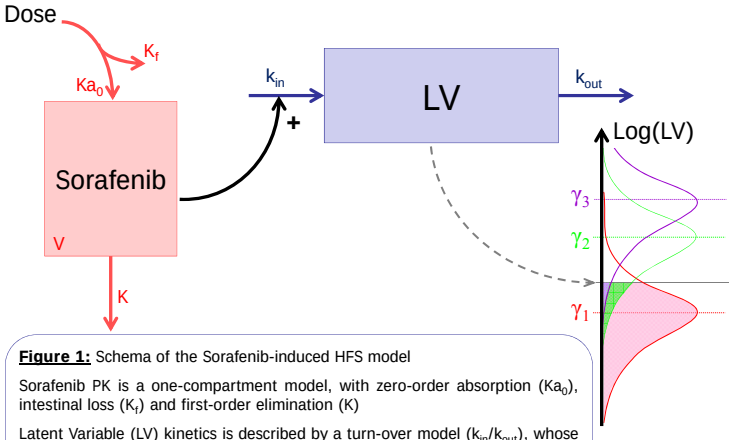


Figure 1: Schema of the Sorafenib-induced HFS model

Sorafenib PK is a one-compartment model, with zero-order absorption (Ka_0), intestinal loss (K_f) and first-order elimination (K)

Latent Variable (LV) kinetics is described by a turn-over model (k_{in}/k_{out}), whose production is stimulated by sorafenib accumulated concentration

Probabilities for HFS grade 1 (red), HFS grade 2 (green), HFS grade 3 (purple) are linked to LV levels according to probit around thresholds (γ_1, γ_2, γ_3)

Impact of sorafenib regimen on HFS dynamics

- Simulation of 100 replicates of 100 individuals per regimen
- Various ‘total daily dose’ and ‘number of administrations per day’

References

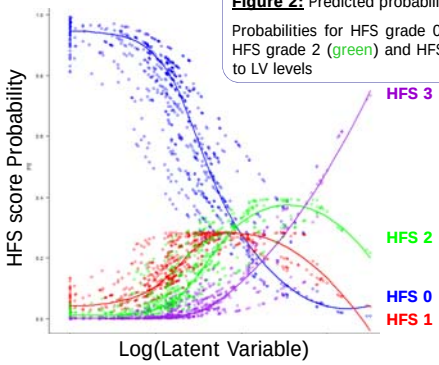
1. Hornecker et al, *Invest New Drugs* 2011
2. Hutmacher et al, J Pharmacokinet Pharmacodyn 2008

Results

- 79% (70/89) patients experienced at least one episode of HFS at any grade, and 31% (28/89) patients experienced at least one grade 3 HFS episode

Figure 2: Predicted probabilities for each HFS score

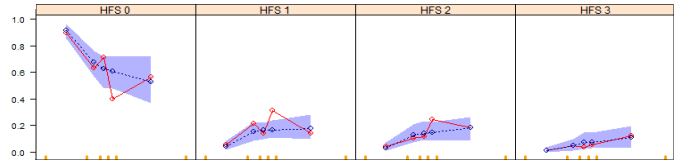
Probabilities for HFS grade 0 (blue), HFS grade 1 (red), HFS grade 2 (green) and HFS grade 3 (purple) according to LV levels



- The latent variable has a half-life of 7 days, whereas sorafenib has a plasma half-life of 35 hours
- Our model allows taking into account the differences between the kinetics of drug concentration, and the kinetics of the toxicity

Figure 3: Visual Predictive Checks of probability of HFS score according to latent variable levels

Probabilities for HFS scores as observed (red), and computed from 100 simulations with associated 95% confidence interval (blue)



- The evolution of HFS probability over time, the duration of HFS episodes, and the number of patients experiencing HFS grade 3 were found to be increased when the total daily dose is split over daytime

Table 1: Percentage of simulated patients (median and 90% confidence interval) experiencing at least one HFS grade 3 episode, under various sorafenib regimen

Regimen	800 mg	600 mg	1200 mg		1600 mg	
	400 x 2	200 x 3	600 x 2	400 x 3	800 x 2	400 x 4
HFS 3	47 [40-53]	51 [42-59]	51 [44-59]	62 [53-71]	55 [47-62]	70 [63-77]

Conclusion and perspectives

- Understanding the dynamic relationship between drug administrations and an induced adverse event is essential to control toxicities and adequately adjust treatment modalities
- Our model suggests that: The more the total daily dose is split, the more the patients are at risk to experience severe HFS