Optimization of sorafenib dosing regimen using the concept of utility

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Introduction

- **Utility Function** allows finding a compromise between drug efficacy and toxicity, balancing the probability of benefit of risks [1,2]
- **Sorafenib** is an oral non-specific multi-kinase inhibitor, approved for the treatment of renal and hepatic carcinoma
- **Tumor Growth Inhibition** (TGI) results from blocking cell proliferation and angiogenesis by targeting Raf/ERK pathway
- **Hand-Foot Syndrome** (HFS) is one of the major dose-limiting toxicity for sorafenib

Objectives

To apply the concept of utility function to determine the optimal regimen of sorafenib integrating pharmacokinetic-pharmacodynamic models for efficacy and toxicity

Methods

Sorafenib PK Model (Hornecker et al [3])

- Sorafenib PK described by a one-compartment model with first-order elimination and saturable absorption (due to intestinal loss)

Sorafenib TGI Model (Hoshino-Yoshino et al [4])

- The efficacy on tumor growth inhibition (TGI) was linked by a sigmoidal model to the area under the unbound concentration curve (AUC_u) at steady state

Sorafenib HFS Model (Hénin et al [5])

- Accumulated sorafenib impacts on the kinetics of a latent variable (LV, interpretable as a non-identified biomarker). Probabilities for each HFS score (0, 1, 2, 3) were computed from a probit function of LV and thresholds (γ)

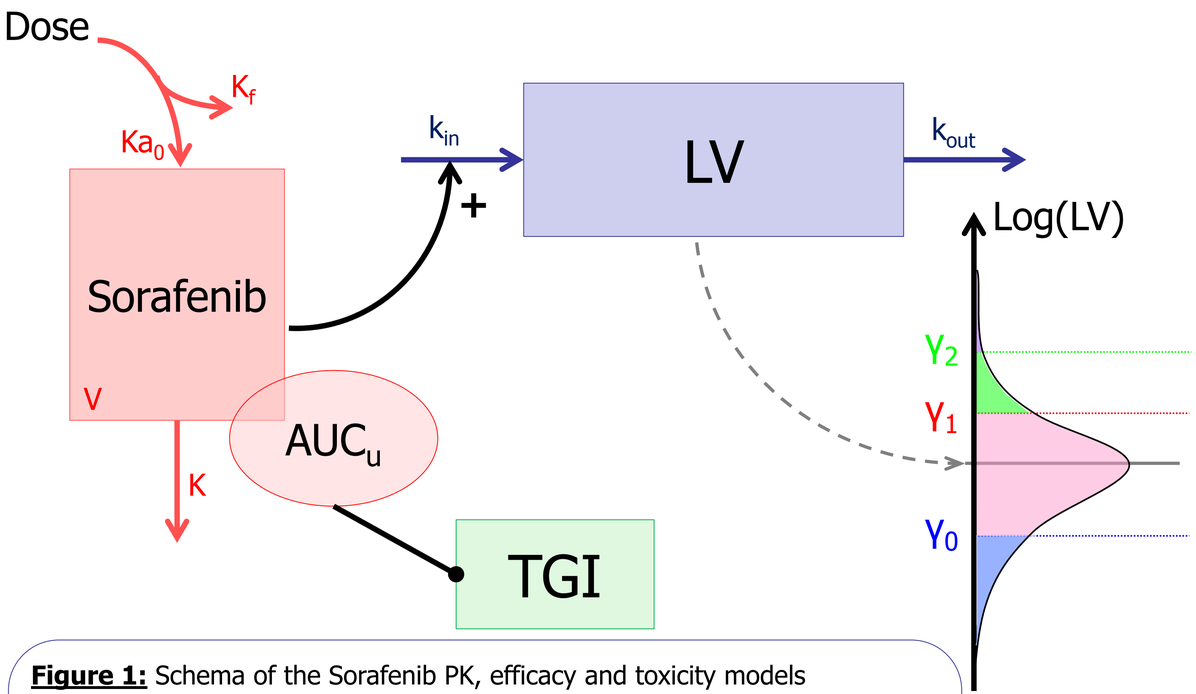

Figure 1: Schema of the Sorafenib PK, efficacy and toxicity models

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 0 (blue), grade 1 (red), grade 2 (green), grade 3 (purple) are linked to LV levels according to probit at thresholds (γ_0,γ_1, γ_2)

Utility Function: $\omega_{eff} \cdot P_{eff} + \omega_{tox} \cdot (1 - P_{tox})$

- **Peff**: proportion of responding patients (**TGI > 20 %**)
- **Ptox**: proportion of patients with untolerable risk (**p(HFS≥2) > 5%**)
- Relative contribution to utility (ω_{eff}**: 60%;** ω_{tox} **: 40%**)
- Utility score computed in 100 replicates of 100-patient populations were simulated for each sorafenib regimen :
  - Daily Amount ranging from 200 to 2000 mg
  - Fractionated in 1, 2, 3, and 4 administrations per day
- Evaluation of sensitivity to thresholds on optimal utility regimen

Results

- Simulations suggest that fractionation has a greater impact on HFS risk than daily dose itself, due to non-linearity in PK
- Evolution of the utility score with *a priori* chosen thresholds (Figure 2)
  - The usual 400mg b.i.d. regimen is among the most utile regimens.
  - with once daily regimen, increased amounts result in a gain in efficacy
  - with fractionated regimens, the utility tends to decrease when the daily amount increases, due to an excess of intolerable risk for HFS

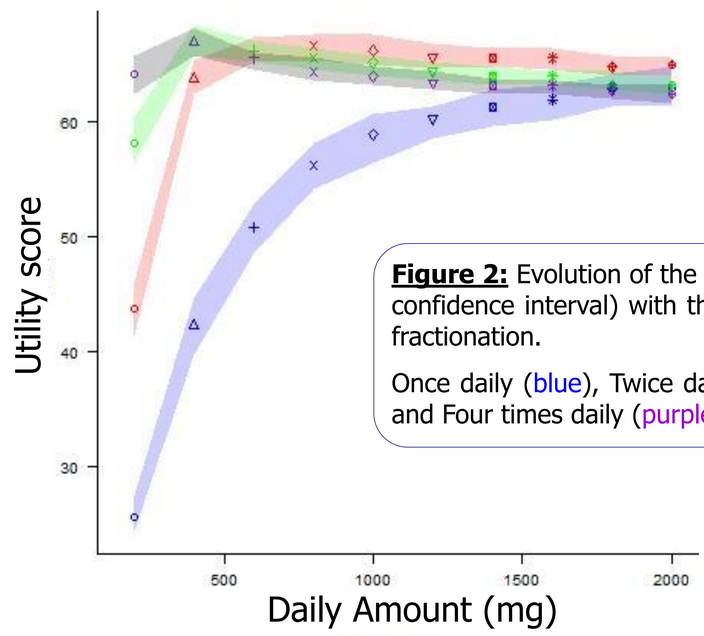

Figure 2: Evolution of the utility score (median and 50% confidence interval) with the daily sorafenib amount and fractionation.

Once daily (blue), Twice daily (red), Thrice daily (green) and Four times daily (purple)

Sensitivity to utility thresholds

- When the thresholds of the utility function are altered, the absolute level of utility of each dosing regimen varies but not the ranking order
  - when efficacy is defined as 20% TGI at least, twice daily administration yields the best utility for daily doses between 500 and 1500 mg, as soon as the risk of intolerable toxicity is higher than 5%
  - when toxicity is defined as 5% risk of intolerable toxicity, an efficacy defined as 10% TGI at least favors once daily dosing, while an efficacy defined as 30 % TGI at least, or higher, favors a three to four times daily dosing regimen.
- A relative contribution 60/40, giving more weight to efficacy, seemed reasonable for anticancer drugs, where a gain in efficacy is often preferred to an increased risk of toxicity.

Conclusion and perspectives

- The concept of utility allowed defining a compromise between the expected gain in efficacy and the enhanced risk of toxicity when increasing the exposure. The choice of the relative contributions and the thresholds is determinant for the interpretation of the utility.
- Taking into account tumor growth inhibition in the utility function, the twice daily administration schedule is favored for daily doses greater than 600 mg.
- The utility is a comprehensible concept for the optimization of dosing regimen, allowing the balance between the required response and acceptable risks. This approach relies on the combination of several PK-PD models, and can be extended to multi-scale models.

References

1. Sheiner et al, Ann N Y Acad Sci 1978
2. Ouellet et al, Clin Pharmacol Ther 2009
3. Hornecker et al, Invest New Drugs 2011
4. Hoshino-Yoshino et al, Drug Metab Pharmacokinet 2011
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