PKPD Modeling of the Angiogenic Factors VEGF, sVEGFR-2, sVEGFR-3 and sKIT following Sunitinib Treatment in GIST

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Background and Objectives

Quantifying relationships between biomarkers and response could potentially improve interpretation of treatment activity and facilitate treatment individualization for anti-angiogenic drugs both during drug development and in clinical practice.

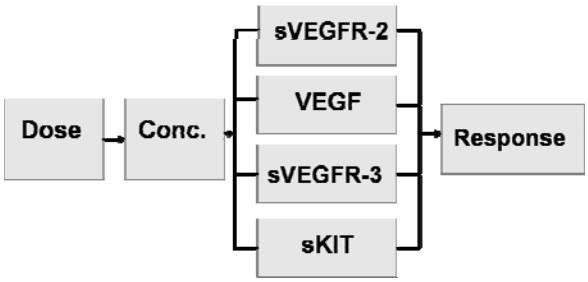

Fig 1. Potential relationships to investigate for the evaluation of angiogenic factors biomarkers following anticancer drug treatment

The aim of the present study was to investigate **dose-exposure-biomarker relationships** following sunitinb (Sutent®) treatment with focus on the potential biomarkers **VEGF, sVEGFR-2, sVEGFR-3 and sKIT**.

Methods

- **Angiogenic factors:** VEGF, s-VEGFR-2, sVEGFR-3, sKIT
- **Study duration:** Up to 85 weeks of treatment
- **Indication:** Gastro intestinal stromal tumors (GIST)
- **Number of patients:** 303
- **Treatment:** Sunitinib - oral tyrosine kinase inhibitor
  Placebo, 4/2:50 mg, 2/1:50 mg,
  2/2: 25,50,75 mg, Cont: 37.5 mg
- NONMEM VI, FOCE INTERACTION
- **PK:** Individual PK parameters [1]
- **PD:** Indirect response models
- **Disease progression:** Symptomatic and protective models

Results

The dose-exposure-biomarkers relationships were described using indirect response models where sunitinib treatment decreased the production of sVEGFR-2, sVEGFR-3 and sKIT and inhibited the degradation of VEGF (Eq. 1, Eq. 2, Table 1).

A linear symptomatic disease progression model with a common slope described the increase of VEGF and sKIT over time in the absence of drug. (Eq. 3)

A common typical IC_{50} parameter for the four biomarkers could be estimated. The individual IC_{50} parameters for VEGF, sVEGFR-2 and sVEGFR-3 were highly correlated (75-92 %).

The predictive performance of the models are illustrated in Fig 2 by visual predictive checks and shows well described dose-exposure-biomarkers relationships .

$$\frac{dy}{dt} = K_{in} \cdot \left(1 - \frac{E_{max} \cdot C}{EC_{50} + C}\right) - K_{out} \cdot y(t) \qquad \text{Eq. 1}$$

$$\frac{dy}{dt} = K_{in} - K_{out} \cdot \left(1 - \frac{E_{max} \cdot C}{EC_{50} + C}\right) \cdot y(t) \qquad \text{Eq. 2}$$

$$DP = Base \cdot (1 + DP_{slope} \cdot Time) \qquad \text{Eq. 3}$$

$$K_{in} = DP \cdot K_{out}$$

Table 1. Parameter estimates

Parameter	VEGF (IIV CV%)	sVEGFR-2 (IIV CV%)	sVEGFR-3 (IIV CV%)	sKIT (IIV CV%)
Base (pg/mL)	59.8 (50)	8660 (19)	63900 (43)	39200 (50)
MRT (days)	3.8 (24)	23.1 (24)	16.7 (24)	101 (27)
IC_{50} (mg/L)	0.04 (50)	0.04 (43)	0.04 (63)	0.04 (240)
Hill	3.31	1.54	-	-
DP_{Slope} ($month^{-1}$)	0.03 (171)			0.03 (172)
Res Error (%)	45	12	22	23
Res Error (pg/mL)	-	583	-	-

MRT = $1/K_{out}$, DP_{slope} = Disease progression

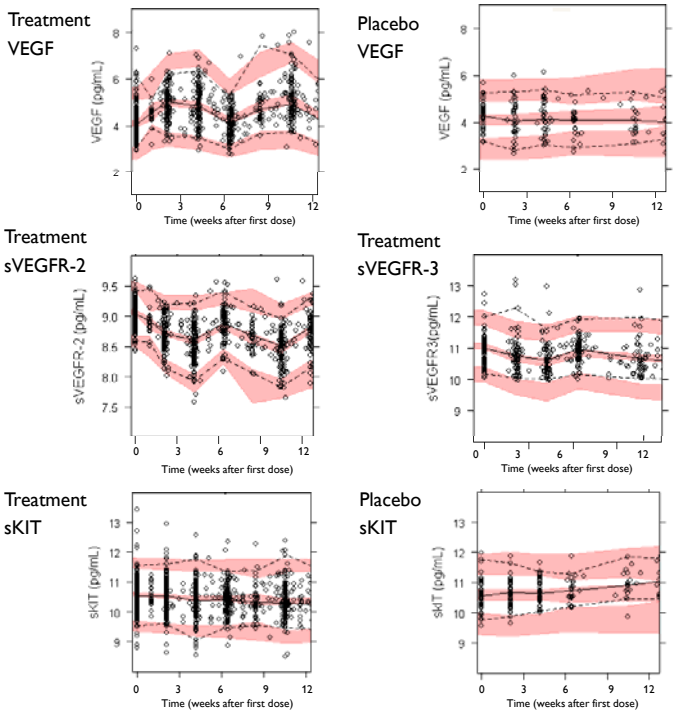

Fig 2. Visual Predictive checks of final models based on 500 simulations. o observed, — median of the observed data, --- 5th and 95th percentiles of the observed data, 95 % confidence intervals based on the simulated data's 5th, 50th and 95th percentile.

Conclusion

The time-courses of the angiogenic factors VEGF, sVEGFR-2, sVEGFR-3 and sKIT following placebo and sunitinib treatment were well characterized.

The high within-patient correlations in IC_{50} indicate that it may be sufficient to measure a limited set of the angiogenic factors for exploring correlations of treatment outcome.

References

[1] Amantea MA., et al., J Clin Oncol 26: 2008 (May 20 suppl; abstr 2522)