PKPD-Modeling of Standard Uptake Value (SUV) in Gastro-Intestinal Stromal Tumors (GIST) patients treated with sunitinib

UPPSALA UNIVERSITET

Emilie Schindler[1], Paul Westwood[1], Michael Amantea[2], Emma K. Hansson[1], Peter A. Milligan[2], Mats O. Karlsson[1], Lena E. Friberg[1]

[1] Department of Pharmaceutical Biosciences, Uppsala University, Sweden, [2] Pfizer Global Research and Development

Introduction

- A change in tumor glucose utilization may be a significantly better predictor of early tumor response and clinical outcome compared with conventional tumor size measurements (RECIST) in patients treated with the multi-targeted tyrosine kinase inhibitor sunitinib [1].
- Tumor glucose metabolism is determined by the maximal standardized uptake value (SUV) assessed by PET after [^{18}F]-fluorodeoxyglucose (FDG) administration and corrected for body weight (***Fig. 1***).

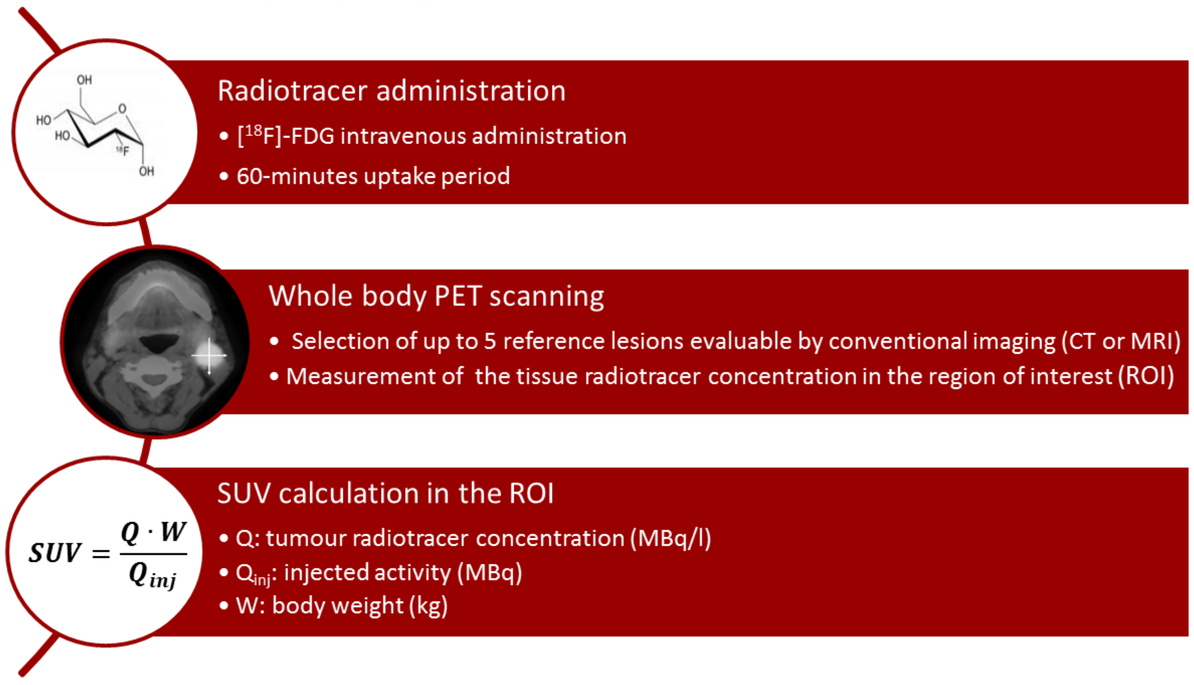


Fig.1: Assessment of SUV by PET scanning after FDG administration.

Objectives

- To characterize the time-course of SUV and investigate potential longitudinal relationships between sunitinib dose, AUC, biomarkers (VEGF, sVEGFR-2 and sKIT), and SUV in patients with gastro-intestinal stromal tumors (GIST).
- To evaluate SUV response as a predictor for overall survival (OS).

Methods

Patients and Data

- 47 patients with imatinib-resistant GIST were followed for a median time of 14 weeks of treatment with three different oral doses (25, 50 and 75 mg/day) of sunitinib under three different treatment schedules.
- SUV measurements (n=158) were available at baseline and up to 94 weeks.
- Individual PK parameters and relative changes from baseline for four biomarkers (VEGF, sVEGFR-2, sVEGFR-3, sKIT) and SLD (sum of longest diameters) were predicted by earlier developed models. [3, 4]

Model Building

- A longitudinal tumor growth inhibition model [2] was used to investigate the relationships between the change in SUV and several predictors (***Fig.2***).
- A parametric time-to-event model based on the Weibull function (Eq.1) was used to evaluate a range of predictors for OS (***Fig.2).***

$$h(t) = \lambda\alpha t^{(\alpha-1)} \cdot e^{(\beta_1 \cdot Predictor_1 + \beta_2 \cdot Predictor_2 + ...)} \quad \text{(Eq.1)}$$

- Censoring was described by a Weibull model.
- Estimations were performed using NONMEM version 7.

SUV model

- Dose(t)
- AUC(t)
- $BM_{REL}(t) = \frac{BM(t) - BM_0}{BM_0}$
- $BM_{REL}(t) = \ln(BM(t)/BM_0)$

Survival analysis

- Dose(t)
- AUC(t)
- BM_0
- $BM_{REL}(t) = \frac{BM(t) - BM_0}{BM_0}$
- SUV_{BASE}
- SUV(t)
- $SUV_{REL}(t) = \frac{SUV(t) - SUV_{BASE}}{SUV_{BASE}}$
- SLD_{BASE}
- $dBP_{REL}(t) = \frac{dBP(t) - dBP_0}{dBP_0}$
- ANC(t)

BM(t): model-predicted timecourse of sKIT, VEGF, sVEGFR-2 (and VEGFR-3 for survival analysis) [3]
BM_0: model-predicted baseline levels of sKIT, VEGF, sVEGFR-2 (and VEGFR-3 for survival analysis) [3]
SUV_{BASE}: observed baseline SUV
SUV(t): model-predicted SUV
SLD_{BASE}: observed baseline SLD [3]
dBP_{REL}: model-predicted relative change in diastolic blood pressure
ANC(t): model-predicted change in absolute neutrophil count

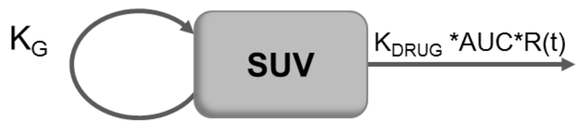
Fig.2: Predictors tested during SUV model development (left) and survival analysis (right).

Predictors were tested one-by-one and in combination.

Results

SUV Model

- The longitudinal SUV data were well characterized by the tumor growth inhibition model (Eq.2, Eq.3) with a fast initial decline in SUV, followed by a more static phase.
- Daily AUC was the best predictor for SUV response and the model showed no additional improvement when adding another predictor.



$$\frac{dy}{dt} = K_G \cdot y(t) - K_{DRUG} \cdot AUC_{0-24} \cdot R(t) \cdot y(t) \quad (Eq.2)$$

$$R(t) = e^{-\lambda t} \quad (Eq.3)$$

Fig.3: Final model describing the SUV data and the corresponding equations. *K_G : SUV increase rate constant; K_{DRUG} : SUV reduction rate constant induced by the drug; λ : resistance appearance rate constant*

Table 1: Final parameter estimates

Parameter	Estimate	RSE (%)	IIV (CV %)	RSE (%)
K_G (wk^{-1})	0.00057	5.2	293	4.0
K_{DRUG} ($wk^{-1} \cdot AUC^{-1}$)	91.9	17	-	-
λ (wk^{-1})	1.19	28	91	17
Residual error (%)	0.36	0.01	-	-

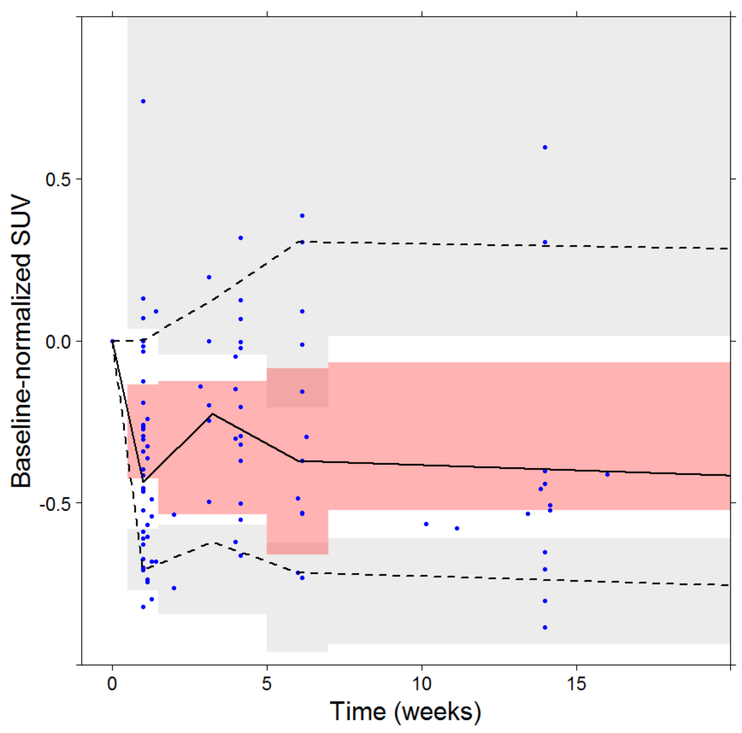


Fig.4: Visual predictive checks for the final SUV model describing the relative change in SUV from baseline vs time. *Median (solid line), 10th and 90th percentiles (dashed lines) of the observed data are compared to the 95% confidence intervals (shaded areas) for the simulated data's 10th, 90th percentiles and median.*

Overall Survival Analysis

- The model-predicted relative sVEGFR-3 change from baseline was the most significant predictor for OS (ΔOFV=-18.8).
- Addition of SUV_{BASE} improved the OFV further (ΔOFV=-3.93) while adding SLD_{BASE} was not significant (ΔOFV=-0.5).

Discussion and Conclusions

- The present results indicate that the daily AUC is predictive of early metabolic tumor response, as determined by SUV.
- In a previous analysis, sKIT was shown to be the best predictor of tumor size [3]. However, because of the rapid SUV response, it is not surprising that sKIT, with a turnover time of 14 weeks, didn't characterize the SUV data.
- Baseline SUV was identified as a predictor of OS and was better than baseline SLD.

References

[1] Prior JO et al. J Clin Oncol (2009) 27 : 439-45
[2] Claret et al. J Clin Oncol (2009) 27 : 4103-4108
[3] Hansson E. et al. PAGE 20 (2011) Abstr 2183 [www.page-meeting.org/?abstract=2183]
[4] Houk B. et al., Clin Cancer Res. 2009 15 : 2497-2506

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° 115156, resources of which are composed of financial contributions from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution. The DDMoRe project is also supported by financial contribution from Academic and SME partners. This work does not necessarily represent the view of all DDMoRe partners.

Drug Disease Model Resources