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

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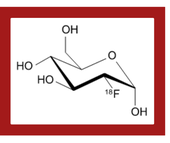
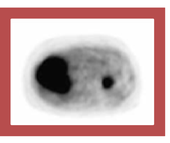
Background and Objectives

- Evaluation of tumor glucose metabolism has been suggested as an alternative to tumor size to assess early tumor response to therapy in cases where clinical benefit is observed but a change in tumor size is limited or delayed (e.g. cytostatic drugs) [1].
- Sunitinib (Sutent®) is a multi-targeted tyrosine kinase inhibitor with anti-angiogenic properties, approved for the treatment of imatinib-resistant or -intolerant gastro-intestinal stromal tumors (GIST).

Radiotracer administration
- [^{18}F]-FDG intravenous administration
- 60-minutes uptake period



Whole body PET/CT scanning
- Selection of **up to 5 lesions** evaluable by CT
- Measurement of radiotracer concentration in the region of interest (ROI)



Standardized uptake value (SUV) calculation in the ROI
- Q: tumor radiotracer concentration in ROI (MBq/l)
- Q_{inj}: injected activity (MBq)
- LBW: lean body weight (kg)

$$SUV = \frac{Q \cdot LBM}{Q_{inj}}$$

Fig.1: FDG-PET scan procedure and SUV calculation

The objectives of the present study are:
- To investigate potential relationships between sunitinib exposure and the time-course of the maximum and mean SUV (SUV_{max} and SUV_{mean} [2]) of individual lesions in GIST patients treated with sunitinib
- To characterize both inter-individual (IIV) and inter-lesion variability (ILV) in SUV responses
- To investigate potential relationships between SUV_{max} and overall survival (OS)

Methods

Patients and Data

Sixty-six imatinib-resistant GIST patients treated with sunitinib were included in the analysis [3].

Table 1: Summary of the data

Dosing schedule (weeks on/off)	6-week cycles (4/2): 50 mg *q.d.* 4-week cycles (2/2): 25, 50, 75 mg *q.d.* 3-week cycles (2/1): 50 mg *q.d.*
Pharmacokinetics	Individual PK parameters for 44 patients [4] Typical values for 22 patients [4]
SUV for individual lesions	607 baseline and post-baseline SUV_{max} and SUV_{mean} data from 172 lesions Up to 5 lesions per patient Median duration of follow-up: 10 weeks Maximum duration of follow-up: 102 weeks

Individual lesion SUV model

- *Structural model:* Indirect response (IDR) models with inhibition of the production (R_{in}) or stimulation of the loss (k_{out}) of response were investigated to describe the time-course of SUV of individual lesions. Linear, power and E_{max} drug-effect relationships driven by the daily dose or the daily AUC were considered during model building. Linear and non-linear disease progression models were tested.
- *ILV model*: The ILV model for a parameter θ_{ij} for the ith individual and the jth lesion can be written as:

$$\theta_{ij} = \theta \cdot \exp(\eta_i + \kappa_{ij})$$

where θ is the typical value in the population, η model between individual differences and κ model between lesion differences, with $\eta \sim N(0, \omega^2)$ and $\kappa_j \sim N(0, \pi_j^2)$. A common variance is assumed between lesions, i.e. $\pi_1^2 = \pi_2^2 = \cdots = \pi_L^2$. Both IIV and ILV were evaluated in all model parameters.

- *Residual error model*: Individual lesions' SUV assessed from the same FDG-PET scan were allowed to have different residual error values (ε), which arose from a multivariate normal distribution parameterized with a zero mean vector and a covariance matrix Σ.
  - ✓ The diagonal elements of Σ containing the variances for each ε were assumed to be the same.
  - ✓ The off-diagonal elements of Σ containing the covariances between ε were assumed to be the same, denoting the same correlation between the SUV of all lesions assessed simultaneously.
  - ✓ This was implemented in NONMEM through a Cholesky decomposition of the sigma matrix and the level-2 (L2) item.
- Model development was performed using SUV_{max} data. The final SUV_{max} structural model was applied to SUV_{mean} data.

Overall survival model

- A parametric time-to-event model was developed to describe the OS data.
  - ✓ Weibull and exponential distributions were evaluated to describe the baseline hazard for OS.
  - ✓ The following predictors were evaluated on OS:
    - Maximum individual lesion SUV_{max} at baseline (observed and predicted)
    - Summed SUV_{max} at baseline (observed and predicted)
    - Summed SUV_{max} time-course
    - Relative change from baseline in summed SUV_{max} over time
    - Maximum relative change in individual lesion SUV_{max} from baseline at week 1 and at week 2
    - Baseline observed tumor size (sum of longest diameters, SLD)
  - ✓ Censoring was described by an exponential model.

Estimation and simulations were performed using NONMEM 7.3.

References

[1] Wahl et al. J Nucl Med. 2009; 50 Suppl 1): p. 122S-50S.
[2] Vanderhoek et al. J Nucl Med. 2013; 54(8): p.1188-94.
[3] Demetri et al. Clin Cancer Res. 2009; 15(18): p. 5902-9.
[4] Houk et al. Clin Cancer Res. 2009; 15(7): p.2497-506.

Acknowledgement 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 financially supported by contributions from Academic and SME partners. This work does not necessarily represent the view of all DDMoRe partners.

Results

Individual lesion SUV model

- Log-transformed individual lesion SUV_{max} data were well described by an IDR model with stimulation of k_{out} through a linear drug effect driven by daily AUC:

$$\frac{dSUV}{dt} = R_{in} - k_{out} \cdot (1 + DRUG \cdot AUC_{daily}) \cdot SUV(t)$$

with $R_{in} = Base \cdot k_{out}$ and $SUV_{t=0} = Base$

- The estimated IIV was larger than the estimated ILV for both SUV_{max} baseline (Base) and the drug effect parameter (DRUG).
- The typical doubling time of SUV_{max} for return to baseline during off-treatment periods was ~2 weeks.
- The model predicts a typical decrease in SUV of 49% after 14 days of sunitinib treatment (50 mg *q.d.*).
- No significant disease progression was identified.
- VPCs illustrate the capability of the model to predict the drug effect on individual lesion SUV_{max} (Figure 2A), as well as the summed SUV_{max} of all lesions (Figure 2B) at each time point.
- In addition, the final structural model successfully described individual lesion SUV_{mean} data.

Table 2: Final parameter estimates for the individual lesion SUV_{max} and SUV_{mean} models

	Individual lesion SUV_{max}			Individual lesion SUV_{mean}		
Parameter	**Typical value (RSE%)**	**IIV CV% (RSE%)**	**ILV CV% (RSE%)**	**Typical value (RSE%)**	**IIV CV% (RSE%)**	**ILV CV% (RSE%)**
Base	7.73 (6)	33 (15)	23 (17)	5.81 (6)	29 (16)	25 (15)
k_{out} (week^{-1})	0.378 (28)	-	-	0.340 (33)	-	-
DRUG (AUC^{-1})	1.03 (18)	60 (33)	51 (21)	1.00 (19)	64 (28)	51 (23)
Residual error (%)	43.0 (16)	-	-	43.5 (15)	-	-

Base: individual lesion SUV baseline value; *DRUG*: SUV reduction rate constant induced by sunitinib; k_{out} : loss of response rate constant; *RSE*: relative standard error.

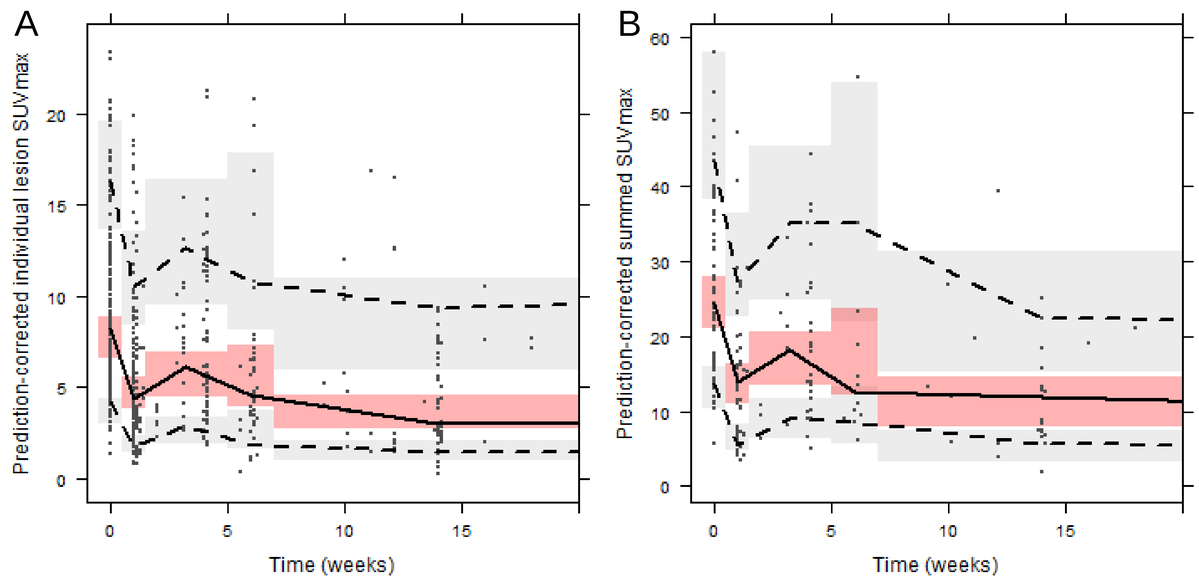


Fig.2: Visual predictive checks of the final individual lesion SUV_{max} model.
(A) Individual lesion SUV_{max} (B) Summed SUV_{max} from all target lesions. *Median (solid line), 10th and 90th percentiles (dashed lines) of the observed data are compared to the 95% confidence intervals (shaded areas) for the median, 10th and 90th percentiles of the simulated data (based on 1000 simulations).*

Overall survival model

- The underlying hazard for OS was best described by an exponential distribution.
- The relative change from baseline in summed SUV_{max} over time was the most significant predictor for OS (dOFV = -25.2), followed by the maximum relative change in individual lesion SUV_{max} from baseline at week 1 (dOFV = -6.0). In both cases, the hazard decreases as the relative reduction in SUV increases.

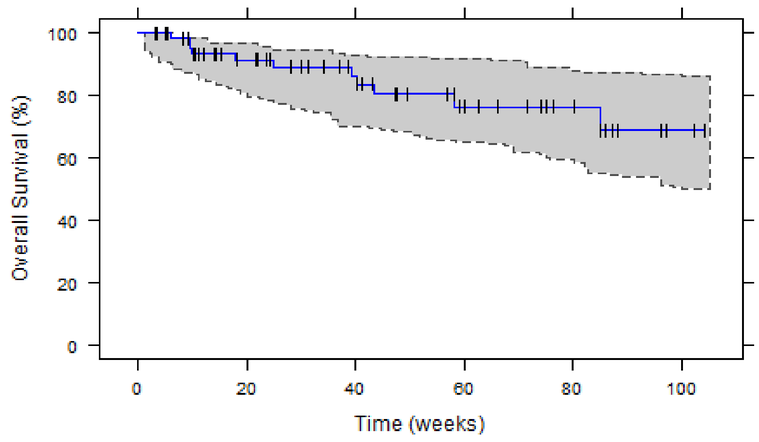


Fig.3: Visual predictive check for the Kaplan-Meier survival curve. *The observed Kaplan-Meier curve (solid line) is compared to the 90% confidence interval (shaded area) derived from model simulations (based on 200 samples) of the survival model including the relative change from baseline in the summed SUV_{max} across lesions. Vertical black lines represent censored observations*

Discussion and Conclusions

- The developed model appropriately described the time-course of individual lesion SUV_{max} and SUV_{mean} in GIST patients treated with sunitinib. Significant IIV and ILV in SUV responses could be identified.
- Preliminary results showed that SUV-based metrics are related to OS, supporting that FDG-PET can be of interest to early predict clinical outcome during treatment.
- This methodology can be used to leverage data collected on individual lesions (e.g. tumor size, volume, metabolic activity) during oncologic clinical trials.

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