Population modeling of uni- and three- dimensional and density-based tumor measurements in gastro-intestinal stromal tumor patients treated with imatinib

Sreenath M. Krishnan[1], Emilie Schindler[1], Gaia Schiavon[2,3], Ron Mathijssen[2], Lena E. Friberg[1]

[1]Department of Pharmaceutical Biosciences, Uppsala University, Sweden. [2] Department of Medical Oncology, Erasmus University Medical Center, Rotterdam, The Netherlands.

[3] *current affiliation:* Translational Science, Oncology iMed, AstraZeneca, Cambridge, UK.

Objectives

- To develop population pharmacodynamic models describing the time-course of maximum trans-axial diameter (MTD), software-calculated segmented volume (V_{actual}), ellipsoidal volume ($V_{ellipsoid}$) and tumor density measurements in imatinib-treated gastro-intestinal stromal tumor (GIST) patients, characterizing the typical trend, inter-individual (IIV) and inter-lesion variability (ILV) in response.
- To investigate model-predicted tumor metrics as predictors of overall survival (OS) and time to treatment failure (TTF).

Background

Tumor density [1] and three-dimensional (3D)-based tumor metrics have been suggested to better discriminate tumor response to treatment than the traditional unidimensional (1D) metrics for GIST which often exhibit non-uniform size changes [2,3].

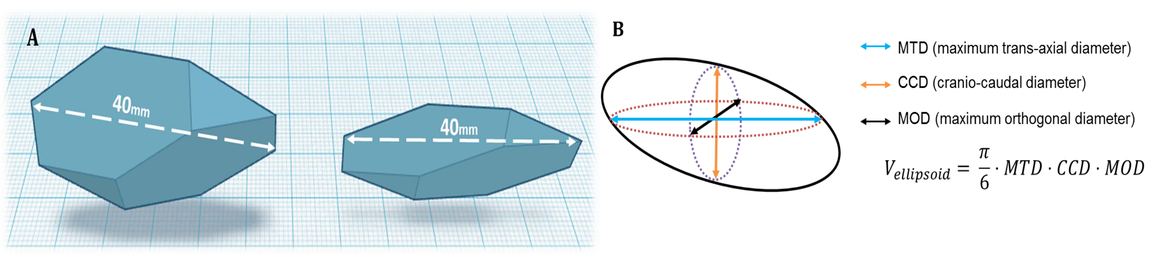

Fig.1 ***[A]*** *An illustrative example showing that tumor volume may significantly decrease during treatment even though MTD may not change.* ***[B]*** *Tumor actual volume may be approximated by the ellipsoidal volume ($V_{ellipsoid}$) calculated based on three orthogonal diameters.*

Methods

Patients and Data

- Data were obtained from a retrospective, non-interventional study involving 77 GIST patients treated with oral imatinib at a starting dose of 400 mg/800 mg q.d. (74/3) [2,3].
- Tumor data from computed tomography (CT) scans were available for 137 lesions (1 – 2 per patient) at baseline and at least one post-baseline visit with median follow-up time of 360 days.
- The observed median (range) OS was 3.06 (0.78 – 9.41) years and TTF was 2.34 (0.25 – 9.08) years.

Model Building

MTD, V_{actual} and $V_{ellipsoid}$ models

- Tumor growth inhibition (TGI) models with exponential [4], constant or Gompertz growth were explored to describe MTD, V_{actual} and $V_{ellipsoid}$ data.
- Linear and non-linear drug effects driven by imatinib daily dose were investigated.

Tumor density model

- Indirect response models (IDR) with inhibition of the production or stimulation of the loss of response were investigated for tumor density.
- Linear and non-linear functions of time were evaluated to describe potential disease progression.

Joint MTD, V_{actual}, $V_{ellipsoid}$ and density model

- The final models of MTD, V_{actual}, $V_{ellipsoid}$ and density were combined into one joint model and the correlations between model parameters were evaluated.

OS and TTF models

- Parametric time-to-event (TTE) models were developed for exploring potential predictors for OS and TTF.
- Constant, exponential, Weibull, Gompertz, log-normal and log-logistic functions were investigated to describe the baseline hazard for OS and TTF.
- The baseline tumor measurements, model-predicted tumor response time-courses, relative change in tumor response at specific time points (1.5, 3, 6 and 12 months) were evaluated alone and in combination as predictors.

Estimations and simulations were performed using NONMEM version 7.3.

Results

MTD, V_{actual} and $V_{ellipsoid}$ models

- TGI models with an exponential growth and a linear dose-driven drug effect that reduces over time best characterized longitudinal MTD, V_{actual} and $V_{ellipsoid}$ (Eq.1).

$$\frac{dy}{dt} = K_G \cdot y(t) - K_{drug} \cdot \frac{Dose}{400} \cdot e^{-\lambda \cdot t} \cdot y(t)$$

- A mixture model described the bimodal distributions of the baseline data and accounted for ILV (not shown).
- The growth rate constants (K_G), drug effect (K_{drug}) and resistance appearance (λ) were specific to each metrics.
- K_G and K_{drug} in all three models (MTD, V_{actual} and $V_{ellipsoid}$) were associated with large IIV but no ILV (Table 1).

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Conclusions

- The developed TGI models adequately described the longitudinal 1D (MTD) and 3D (V_{actual} and $V_{ellipsoid}$) tumor data of liver metastases in imatinib-treated GIST patients.
- An IDR model described the tumor density data that typically decrease during imatinib treatment.
- ILV was identified in the drug effect related to density but not to MTD, V_{actual}, $V_{ellipsoid}$.
- Smaller MTD at baseline were associated with longer OS and TTF. Moreover, a larger decrease in MTD at 6 months was predictive of a longer OS and a larger decrease in $V_{ellipsoid}$ at 3 months of a longer TTF.

Table 1. Final parameter estimates for the MTD, V_{actual} and $V_{ellipsoid}$ models

	MTD		V_{actual}		$V_{ellipsoid}$	
Parameter (unit)	Typical value (RSE%)	IIV -CV% (RSE%)	Typical value (RSE%)	IIV -CV% (RSE%)	Typical value (RSE%)	IIV -CV% (RSE%)
K_G (week^{-1})	0.00151 (45)	152 (21)	0.00911 (8)	113 (14)	0.0101 (23)	105 (14)
λ (week^{-1})	0.0455 (31)	-	0.0443 (30)	-	0.0448 (20)	-
K_{drug} (400mg^{-1} · week^{-1})	0.0120 (33)	78 (20)	0.0527 (38)	58 (29)	0.0576 (15)	43 (21)
RUV (%)	14 (6)	-	37 (8)	-	43 (6)	-

CV, coefficient of variation; IIV, inter-individual variability; RSE, relative standard error; K_G, growth rate constant ; λ, resistance appearance rate constant; K_{drug}, tumor size reduction rate constant; RUV, residual unexplained variability

Tumor density model

- An IDR model with stimulation of the loss of response through a linear drug effect best described tumor density data (Eq. 2).

Where,

$$\frac{dA}{dt} = R_{in} - k_{out} \cdot A(t) \cdot \left(1 + K_D \cdot \frac{Dose}{400}\right) \quad (2)$$

$$R_{in} = k_{out} \cdot A_0 \quad (3)$$

- IIV and ILV were identified in the drug effect parameter (K_D) and baseline density (A_0) (Table 2).

Table 2. Final parameter estimates for the tumor density model

Parameter (Unit)	Typical value (RSE%)	IIV -CV% (RSE%)	ILV -CV% (RSE%)
A_0 (HU)	59.3 (6)	30 (10)	18 (19)
k_{out} (week^{-1})	0.0942 (33)	-	-
K_D (400mg^{-1} · week^{-1})	1.07 (29)	120 (17)	53 (38)
RUV (%)	20.6 (7)	-	

CV, coefficient of variation; IIV, inter-individual variability; ILV, inter-lesion variability; RSE, relative standard error; A_0, baseline density; k_{out}, rate of loss of response; K_D, density reduction rate constant; RUV, residual unexplained variability

Joint MTD, V_{actual}, $V_{ellipsoid}$ and density model

- No significant correlations were identified between tumor density model parameters and MTD, V_{actual} or $V_{ellipsoid}$ model parameters (<20%).
- High correlations (>99%) were estimated between MTD, V_{actual} and $V_{ellipsoid}$ model parameters.

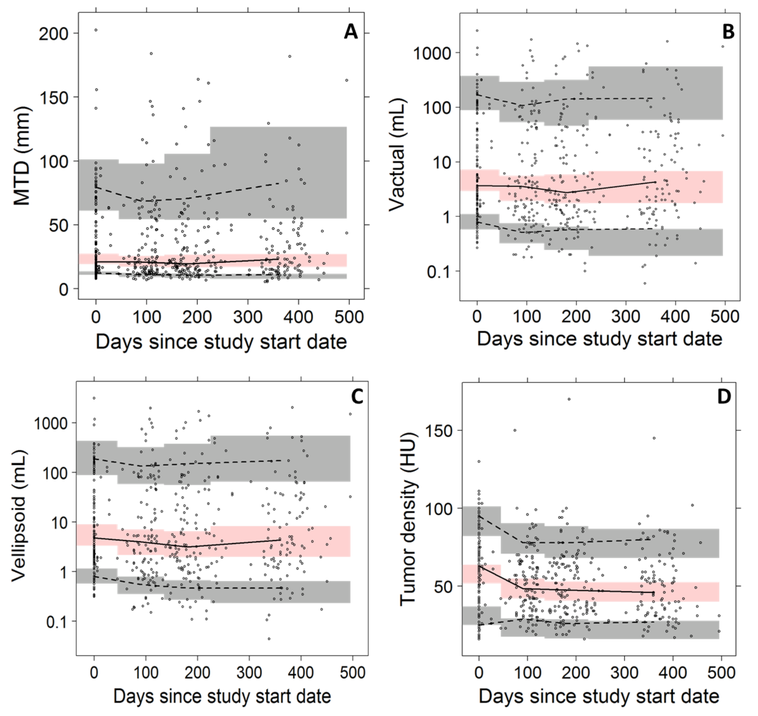

Fig.2. Visual predictive checks of the joint MTD, V_{actual}, $V_{ellipsoid}$ and density models based on 1000 simulations. Median (solid line), 10th and 90th percentiles (dashed lines) of the observed data are compared to the 95% confidence intervals (shaded areas) for the median, 10th and 90th percentiles of the simulated data.

Panels:
[A] *Mean trans-axial diameter (MTD) model;* ***[B]*** *Software calculated segmented volume (V_{actual}) model;* ***[C]*** *Calculated ellipsoidal volume ($V_{ellipsoid}$) model;* ***[D]*** *Tumor density model.*

OS and TTF analysis

- The baseline hazard for both OS and TTF was best described by a Weibull function. Simultaneously, censoring from OS was described by a lognormal distribution and censoring from TTF by a Gompertz distribution.
- In the multivariate analysis, statistically significant predictors (p<0.01) of OS included baseline MTD (hazard ratio (HR) = 1.24 for every 10 mm increase) and relative MTD change from baseline at 6 months (HR = 1.03 for 10% increase from baseline).
- Statistically significant predictors (p<0.01) of TTF included baseline MTD (HR = 1.16 for every 10 mm increase) and relative $V_{ellipsoid}$ change from baseline at 3 months (HR = 1.03 for 10% increase from baseline).
- These findings will be validated in a simultaneous analysis of tumor and OS or TTF data and could guide clinicians in the management of patients during imatinib therapy.

References

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