Dried blood spot sampling for therapeutic drug monitoring of pazopanib

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Introduction

- Pazopanib is an oral multi-targeted tyrosine kinase inhibitor (TKI) used for the treatment of metastatic renal cell carcinoma (mRCC) and metastatic soft tissue sarcoma (STS)
- The optimal therapeutic window for pazopanib in patients with mRCC lies between a C_{trough} level of 20.5 - 36 mg/L
- Patients treated with pazopanib show a high variability in pharmacokinetics (PK)
- Therapeutic drug monitoring (TDM) could therefore be useful to optimize the efficacy and minimize the toxicity of therapy
- At present, pazopanib concentrations are monitored in plasma collected by venous sampling
- Compared to venous sampling, dried blood spot (DBS) sampling is a convenient, simple, flexible and more patient friendly alternative to collect blood in an at home setting

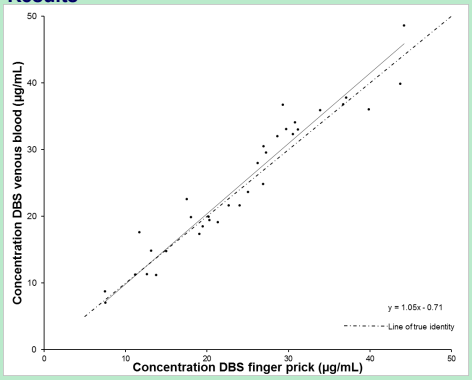
Objective

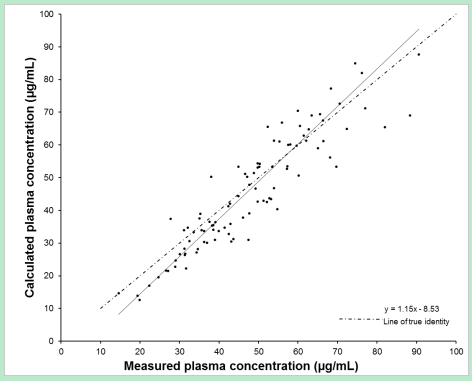
To determine the agreement between pazopanib DBS- and plasma concentrations in order to facilitate the future implementation of pazopanib DBS sampling into clinical practice.

Methods

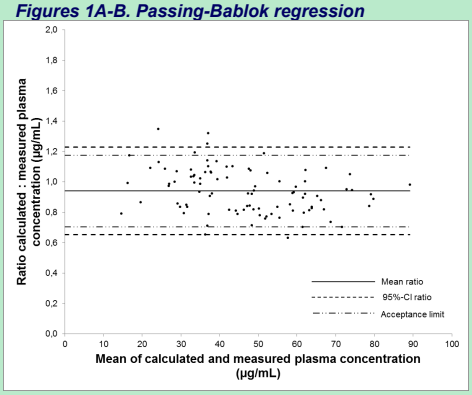
- At day 14 of standard 800 mg once daily pazopanib therapy, patients were admitted to the hospital for pharmacokinetic sampling
- EDTA-blood samples were collected by venepuncture pre-dose and 1, 2, 3, 4, 6, 8, 10 and 24 hours after pazopanib intake; 15 µL blood was collected into an EDTA capillary tube and spotted onto a pre-marked circle on a Whatman FTA® DBS card
- In addition, DBS sampling cards prepared by finger prick were collected pre-dose, and 3 and 8 hours after pazopanib
- Finger prick DBS cards (n=3), venous DBS cards (n=9) and plasma samples (n=9) were all sent to GlaxoSmithKline, USA for further bio-analytical analysis with a validated LC-MS/MS method
- Plasma concentrations were calculated using the previously described formula: plasma concentration = DBSconcentration /(1-haematocrit)
- Plasma concentrations were calculated using both patient specific measured haematocrit values and fixed haematocrit values of 0.40 and 0.45 for males and females
- Passing-Bablok regression and Bland-Altman analysis were used to determine the agreement between the two sampling methods
- We predefined the clinical acceptance limit of the Bland-Altman analysis at a 25% interval around the found ratio

Results





Figures 1A-B. Passing-Bablok regression



Figures 2. Bland-Altman anlysis

Clinical decision making based on C_{trough} levels

Measured plasma C_{trough} level	Calculated plasma C_{trough} level using patient specific haematocrit	
	< 20.5 µg/mL	≥ 20.5 µg/mL
< 20.5 µg/mL	2	0
≥ 20.5 µg/mL	**1**	8

In **bold** a difference in clinical decision making based on calculated and measured plasma C_{trough} levels

Table 1. Clinical decision making

In Table 1, it is shown that in 1 case (9.1%), there would have been a difference in decision making based on measured and calculated plasma concentrations. All other cases of clinical decision making would have been the same based on either the measured or calculated plasma concentration

Discussion

- The present study shows that pazopanib plasma concentrations calculated with the use of DBS, are in good agreement with actually measured pazopanib plasma concentrations
- DBS sampling can be used as an alternative sampling strategy for the determination of plasma concentrations to monitor pazopanib therapy
- A small constant and slightly proportional bias was shown between calculated and measured pazopanib plasma concentrations
- However, these biases are clinically not relevant as the vast majority of data points are within the predefined clinical acceptance limits of the Bland-Altman analysis
- Calculated plasma concentrations using fixed vs measured haematocrit were compared and no significant difference between the plasma concentrations wes observed.
- This indicates that fixed haematocrit values can be used instead of measured haematocrit values when patient haematocrit levels are within the normal ranges
- A limitation of this present study is that DBS cards were prepared by the research nurse
- This makes validation of clinical utility with DBS cards prepared by patients themselves necessary

Conclusions

- **This study shows a good agreement between pazopanib levels measured in plasma and calculated plasma concentrations based on DBS sample collection**
- **DBS could therefore be a very useful and patient friendly approach to monitor pazopanib therapy**
- **The preparation of DBS cards by patients themselves should be validated, before the implementation of DBS into clinical practice**

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