Influence of Non-Adherence on the Estimation of Pharmacokinetic Parameters of Cabozantinib in Renal Cell Carcinoma

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Introduction and Aim

Oral anticancer drugs, such as tyrosine kinase inhibitors (TKIs), are an integral part of modern cancer treatment; however, they require a high degree of personal responsibility from patients regarding correct medication intake. Adequate adherence is of crucial importance in this context.

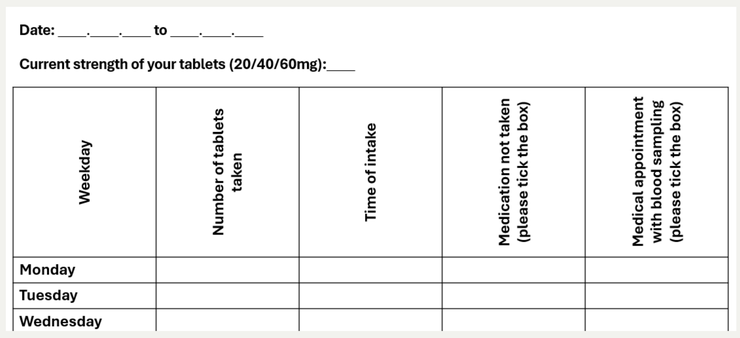
In the prospective, multicentre ON-TARGET study, therapeutic drug monitoring was established for the two TKIs axitinib and cabozantinib in patients with renal cell carcinoma [1]. The aim of this project is to investigate the influence of non-adherence on the estimation of pharmacokinetic (PK) parameters of cabozantinib.

Methods

Documentation

Study site:
- Treatment
- Blood sampling

Patients:
- Recording of medication intake in diaries


Date: ___.___.___ to ___.___.___

Current strength of your tablets (20/40/60mg):___

Weekday	Number of tablets taken	Time of intake	Medication not taken (please tick the box)	Medical appointment with blood sampling (please tick the box)
Monday				
Tuesday				
Wednesday				

Adherence assessment

Criteria for Non-Adherence
- Discrepancy between diary entry and documentation at study site
- Dosing interval <12h
- Number of tablets taken >0 + „medication not taken“ ticked

Used datasets

Dataset A: Clearly documented diary entries
Dataset B: All diary entries

Calculation of adherence
- Overall adherence (OA): % of prescribed tablets taken
- Daily adherence (DA): % of days with correct intake

Estimation of PK parameters of non-adherent individuals

- Identification of patients with non-adherent behaviour within 15 d prior to blood sampling
- Bayesian post-hoc estimation of individual PK parameters [2]
  - Assumed 100% adherence
  - Diary-corrected adherence
- Comparison of PK parameter estimates
- Simulation of the concentration-time profiles

Covariate analysis

- Tested covariate: Average daily adherence till day of blood sampling as continuous, time-dependent covariate on apparent clearance (CL/F)
  - **ADH_A**: Adherence based on dataset A
  - **ADH_B**: Adherence based on dataset B
- Statistically significant if ΔOFV ≥ 3.84, corresponding to $p < 0.05$

Conclusion

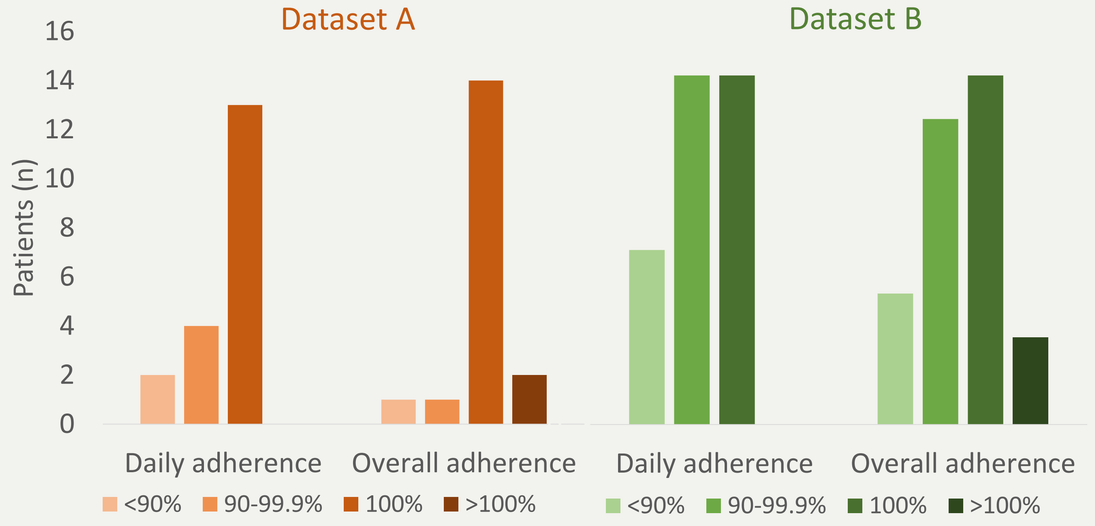
- Patients with renal cell carcinoma receiving cabozantinib in the ON-TARGET study showed high adherence, with a median daily adherence of >98% and a mean overall adherence of >95%.
- Accounting for non-adherence improved the accuracy of PK predictions and may help explain discrepancies between predicted and observed plasma concentrations in the context of therapeutic drug monitoring.
- Adherence was identified as a statistically significant covariate on CL/F. However, the magnitude of the effect was small.

Results

Patient diaries

Patients (m, f)	20 (16, 4)
Observation period	03/2021-12/2024
Total number of diaries analysed	231
Diaries per patient, median (range)	6 (2 - 43)
Daily adherence (%), Median (IQR)	100 (98.1 – 100) or 98.8 (92.7 – 100)
Overall adherence (%), Mean ± SD	98.8 ± 12.1 or 95.8 ± 11.8

Analysis of patient diaries



Estimation of PK parameters of non-adherent individuals

Affected: 12 measured concentrations from 4 patients

	Assumed 100% adherence	Diary-corrected adherence
MAE (concentration)	141.84 ng/mL	113.58 ng/mL
rMPE (%)	13.98	11.74
MAPE (%)	29.70	24.23
Clearance (L/h)	1.99	1.97
Volume of distribution (L)	146.93	143.02

MAE Mean absolute error, rMPE Relative mean prediction error, MAPE Mean absolute percentage error

Covariate analysis

	ADH_A		ADH_B	
	Estimate	Bootstrap, mean (95% CI)	Estimate	Bootstrap, mean (95% CI)
CL	3.87	3.95 (3.06 – 4.79)	3.75	3.92 (2.96 – 4.78)
ADH	4.56	6.54 (1.87 – 35.16)	0.731	1.42 (0.39 – 7.94)
IIV(CL)	0.33	0.30 (0.08 – 0.66)	0.36	0.32 (0.07 – 0.66)
ΔOFV	-19.35		-7.15	

ADH Adherence, IIV Interindividual variability, OFV Objective function value

References

1. McLaughlin AM, Schmulenson E, Teplytska O, et al. Cancers (Basel) 2021; 13.
2. Nguyen L, Chapel S, Tran BD et al. J Clin Pharmacol 2019; 59: 1551–61.

Acknowledgements

We would like to thank all the patients who took part in our project despite their difficult circumstances, as well as all the staff at the study centres for their support.