Original Study

Check for updates

Full text of articles are available online at www.clinical-genitourinary-cancer.com

Axitinib Trough Concentration and its Influence on the Efficacy and Toxicity of Second-line Renal Cell Carcinoma Treatment

Zuzanna Synowiec,[1] Katarzyna Sobańska,[2] Tomasz Synowiec,[3] Artur Teżyk,[4] Piotr Tomczak,[5] Anna Jabłecka[6]

Keywords: Treatment efficacy, Treatment safety, Trough level, Therapeutic drug monitoring, Tyrosine kinase inhibitors

Scan the QR to view the full-text article on the journal website

Abstract

The aim of the article was to study relationships between the axitinib steady-state trough concentration (C_{trough}) and treatment efficacy and toxicity. There was a statistically significant differences between measured axitinib C_{trough} value and treatment response, median progression-free survival, and toxicity in the group of 35 patients. The data collected may be used to determine indications for axitinib therapy monitoring based on C_{trough} measurements.

Introduction: There are known correlations between axitinib exposure and treatment response. The aim of the article was to study relationships between the axitinib steady-state trough concentration and the treatment efficacy and toxicity. **Patients and methods:** 35 patients (24 men and 11 women), treated or initiating treatment with axitinib, were included in the study over the period 2016-2019. Blood samples were collected following 2 weeks of treatment (in patients who initiated the therapy) and at the end of Cycles 1, 2, and 3 thereafter (in the entire study population). For concentration measurements, high-performance liquid chromatography - mass spectrometry (HPLC-MS) was applied. Treatment efficacy was assessed according to the RECIST 1.1 criteria. Therapy toxicity was evaluated according to the CTCAE criteria. **Results:** A statistically significant relationship between the first measured axitinib trough concentration ($C_{trough\ first}$) value and treatment response ($P = .004$) as well as the median progression-free survival (mPFS) ($P = .003$) was observed. The association between axitinib $C_{trough\ first}$ and the median overall survival (mOS) was not statistically significant ($P = .142$). A statistically significant relationship was observed between the mean trough concentration from 3-month observation ($C_{trough\ 1\text{-}3m}$) and treatment response ($P = .008$) as well as mPFS ($P = .001$), without a significant relationship for mOS ($P = .097$). At least grade 3 adverse reactions were meaningfully associated with $C_{trough\ first}$ ($P = .012$) and $C_{trough\ 1\text{-}3m}$ ($P = .003$). **Conclusion:** There are significant relationships between axitinib C_{trough} and treatment response, PFS, and grade ≥ 3 toxicity. The data collected may be used to determine indications for axitinib therapy monitoring based on C_{trough} measurements.

Clinical Genitourinary Cancer, Vol. 20, No. 4, 390.e1–390.e8 © 2022 Elsevier Inc. All rights reserved.

[1]Department of Oncology and Immunooncology, Greater Poland Cancer Centre, Poznan, Poland
[2]Department of Clinical Pharmacy and Biopharmacy, Poznan University of Medical Sciences, Poznan, Poland
[3]Department of Vascular and Endovascular Surgery, Angiology and Phlebology, Poznan University of Medical Sciences, Poznan, Poland
[4]Department of Forensic Medicine, Poznan University of Medical Sciences, Poznan, Poland
[5]Department of Oncology, Poznan University of Medical Sciences, Poznan, Poland
[6]Departemnt of Clinical Pharmacology, Poznan University of Medical Sciences, Poznan, Poland

Submitted: Jun 26, 2021; Revised: Feb 18, 2022; Accepted: Mar 6, 2022; Epub: 12 March 2022

Address for correspondence: Zuzanna Synowiec, MD, Department of Oncology and Immunooncology, Greater Poland Cancer Centre, Radlowa 5a/2, Poznan 61-602, Poland
E-mail contact: md.zuzanna.synowiec@gmail.com

1558-7673/$ - see front matter © 2022 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.clgc.2022.03.006

Introduction

Axitinib is a tyrosine kinase inhibitor (TKI) of the vascular endothelial growth factor (VEGF) receptors VEGFR-1, VEGFR-2 and VEGFR-3. It is approved for first line renal cell carcinoma treatment in combination with check point inhibitors and is an option for second line. Its efficacy in second-line metastatic renal-cell carcinoma (mRCC) treatment has been proved in AXIS phase III trial.[1] The efficacy in first-line treatment has been demonstrated in the KEYNOTE-426 (in combination with pembrolizumab)[2] and JAVELIN Renal 101 (in combination with avelumab) trials.[3] Similarly to other molecularly targeted therapies, axitinib is administered at a fixed starting dose; however, interpatient variability regarding the blood concentration of the drug is observed among patients. This variability may affect axitinib treatment outcomes and therapy toxicity.

Correlations between axitinib exposure and therapy efficacy have been evaluated in the analysis of phase II and phase III trials.[4] To date, such correlations and the values for axitinib monitored therapy have been mainly described based on the area under the curve (AUC) values.[5] No reports assessing a relationship between axitinib trough concentration (C_{trough}) and treatment efficacy and toxicity are available except the article presented by Tsuchiya et al.[6]

The aim of the study was to assess the relationship between axitinib C_{trough} and treatment efficacy and safety in a group of patients receiving this drug in second-line mRCC treatment. The study population included patients who progressed on first-line sunitinib, pazopanib or interferon-alfa treatment. The intervention proposed to the patients included collecting plasma samples during the treatment. There were no treatment interventions based on axitinib concentration measurements during the study. The outcome was measured as a response to the treatment according to RECIST 1.1. criteria[7] and severity of adverse events were assessed based on CTCAE criteria.[8] Progression-free survival (PFS) and overall survival (OS) were defined based on response to the treatment and survival data. Blood samples collection was conducted from 2016 to 2019, whereas study group observation was continued until 2020. The retrospective analysis of relationships between treatment outcome, toxicity and C_{trough} of axitinib was conducted.

Material and Methods

The inclusion criteria were as follows: axitinib treatment as the second-line mRCC therapy, the ECOG performance status score 0-1, adequate organ functioning, and a measurable disease according to the RECIST 1.1 criteria.[7] All patients received axitinib 5 mg twice daily (BID). After 2 weeks of therapy, providing absence of adverse reactions, elevated blood pressure >150/90 mm Hg and anti–hypertensive treatment, the dose could be increased to 7 mg BID, followed by 10 mg BID after subsequent 2 weeks with the same criteria maintained. When unacceptable toxicity was observed, the dose could be reduced to 3 mg BID and further to 2 mg BID.[2]

Between June 2016 and February 2019, 35 patients (24 men and 11 women) treated with axitinib were eligible for the study. All of them provided written informed consent before any trial procedure. The study design was approved by the local medical ethical board. The study group characteristics are provided in Table 1.

Treatment outcome was assessed based on CT scans performed every 3 months. The treatment response was assessed according to the RECIST 1.1 criteria.[7] Toxicity was evaluated based on the medical history, physical exam, and laboratory findings as per the CTCAE criteria.[8]

After inclusion in the study, blood samples were collected monthly during the first 3 months, and every 3 months thereafter providing the patient continued the study treatment. Concerning the patients who initiated the therapy, blood was also collected following 2 weeks of the treatment.

According to the criteria for steady-state achievement and the period of distribution equilibrium, blood was collected after at least 4-5 half-lives of the drug ($T_{1/2}$ 2.5-6.1 hours for axitinib) immediately before the next dosing. Blood was sampled into heparin tubes. The samples were centrifuged for 10 minutes at 4°C (2880 g). Plasma was transferred into Eppendorf amber tubes to protect it from light and stored at -80°C until testing. The axitinib C_{trough} was determined by means of high-performance liquid chromatography - mass spectrometry. The lower limit of quantification (LLoQ) was 0.5 ng/mL. Calibration curves were plotted within the concentration range of 0.5-30 ng/mL (r > 0.995). Consistently with the European Medicines Agency (EMA) validation guidelines, the precision and accuracy of the analytical method were validated. Calculations and automated integration of signals were performed by means of MassHunter Quantitative Analysis Software (*Agilen Technologies, USA*).

The data were analysed using IBM SPSS Statistics 25.0. PFS and OS were estimated using the Kaplan-Meier method. The statistical analysis was based on the Kruskal-Wallis H test to find possible differences in drug concentrations between groups responded differently to the treatment. To find more detailed differences, a post hoc analysis was performed (Dunn's test with Bonferroni correction). The Mann–Whitney *U* test was used to measure relationships between PFS, OS and axitinib trough concentrations: $C_{trough\ first}$ and $C_{trough\ 1\text{-}3m.}$ The same way was used to measure relationships between at least G3 toxicity occurrence and $C_{trough\ first}$ and $C_{trough\ 1\text{-}3m.}$

Results

In the study group, the median progression-free survival (mPFS) and the median overall survival (mOS) were determined: 5 months (range: 1.0-57.0 months) and 25 months (range: 2.0-58.0 months), respectively (Figure 1). The objective response rate was 17.6%. Six patients achieved partial response (PR), and stable disease was observed in 18 patients (51.43%). Progressive disease (PD) was reported in 11 patients (31.43%) as the best response.

Table 1 Characteristics of Axitinib-treated Patients

Patient characteristics	Value (n = 35)	%
Age (y)		
median (range)	64 (38-73)	-
Gender (n)		
Male	24	67.6
Female	11	32.4
BMI (kg/m^2)		
median (range)	28.6 (19.5-41.8)	-
MSKCC 0/1-2/3-5		
Favorable	11	31.4
Intermediate	22	62.9
Poor	2	5.7
IMDC 0/1-2/3-6		
Favorable	9	25.7
Intermediate	24	68.6
Poor	2	5.7
Fuhrman nuclear grade		
2-Jan	18	51.4
3-4/ no data	17	48.6
Prior nephrectomy	35	100
Metastatic sites, n %		
1	2	5.7
≥ 2	33	94.3
Site of metastasis, n %		
Lung	20	57.1
Bone	9	26.5
Liver	17	50
Lymph nodes	20	57.1
CNS	3	14.7
Adrenal	13	37.1
Local recurrence	12	35.3
ECOG		
0	22	62.9
1	13	37.1
1st line treatment		
sunitinib	30	85.7
pazopanib	4	11.4
cytokine	1	2.9

MSKCC, Memorial Sloan Kettering Cancer Center; IMDC, International Metastatic RCC Database Consortium; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group.

Grades 1-2 adverse reactions occurred in the entire study group, while Grade ≥ 3 reactions were reported in 60% of patients throughout the overall period of axitinib treatment. The 10 most common adverse reactions observed during axitinib therapy are listed in Table 2.

C_{trough} values in the tested blood samples ranged from < 0.5 ng/mL to 7.88 ng/mL. In 6 cases, diagnostic values of the drug blood concentration were not obtained. One patient was excluded from the analysis due to failing to meet the scheduled blood collection time. The other 5 patients experienced early disease progression (4 of them at the first radiology assessment and 1 patient at the second assessment but with larger metastatic lesions as early as at 3 months of treatment). They were not excluded from the study, because they represent the significant group of patients with a lack of response to the treatment. For analysis purposes, the concentration value in this group of 5 patients was assumed to be 0 ng/mL.

Relationships between the treatment outcomes in the study group (the best response, PFS, and OS) as well as toxicity of at least grade 3 and the first measured value of C_{trough} ($C_{trough\ first}$) and the mean value from 3-month treatment ($C_{trough\ 1\text{-}3m}$) were assessed. The mean values

Figure 1 (A) PFS in the entire population. (B) OS in the entire population.

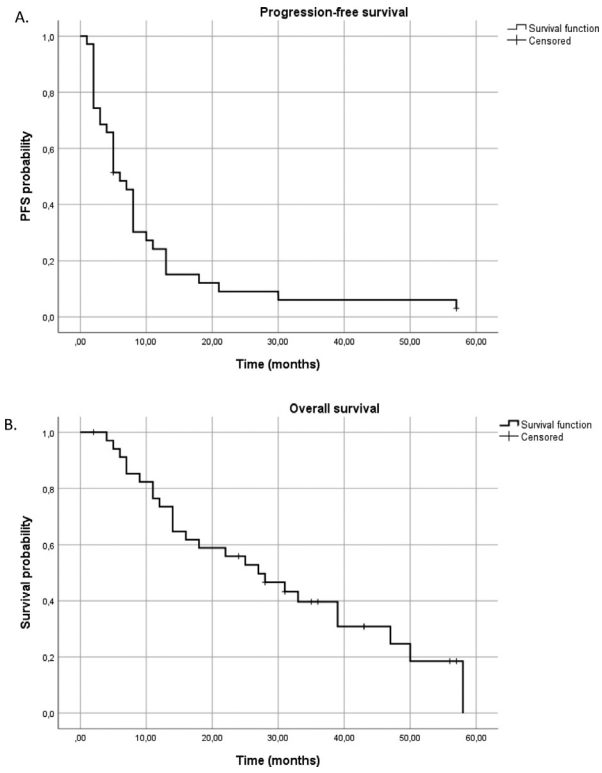

Table 2 The Most Common Adverse Reactions Observed in the Study Group

Adverse event	All grades	%	G1-2	%	G3-4	%
Hypertension	31	88.6	18	51.4	13	37.1
Fatigue	26	74.3	21	60.0	5	14.3
Diarrhea	23	65.7	19	54.3	4	11.4
Hypothyroidism	21	60.0	21	60.0	0	0
Lose weight	21	60.0	21	60.0	0	0
Proteinuria	18	51.4	18	51.4	0	0
Hoarseness	16	45.7	16	45.7	0	0
Decrease appetite	15	42.9	15	42.9	0	0
Hand-Foot Skin Syndrome	12	34.3	9	25.7	3	8.6
Mucositis/Stomatitis	11	31.4	10	28.6	1	2.9

were analysed due to observed intrapatient variability of the C_{trough} values during the treatment. The coefficient of variation (CV) was 57% (range: 3%-99%). It was assessed for 25 patients who had at least 2 diagnostic C_{trough} measurements performed.

A statistically significant difference between $C_{trough\ first}$, $C_{trough\ 1\text{-}3m}$, and radiological response was observed in the study. The *post-hoc* analysis showed the largest differences in $C_{trough\ first}$ and $C_{trough\ 1\text{-}3m}$ values between the groups achieving the best response at the levels of PR or PD (Table 3, Figure 2).

The concentration parameters of interest were compared depending on the PFS and OS values. The C_{trough} values significantly differed between the patients achieving PFS < the median value compared to the group achieving PFS ≥ the median value of 5 months. No OS-related significant differences were observed between groups achieving OS < median value (25 months) compared to the group achieving OS ≥ 25 months. In addition, occurrence of at least grade 3 toxicity was considered as statistically significant. The results are presented in Table 4.

Figure 2 (A) Best response according to axitinib trough concentration at first measurement. (B) Best response according to mean axitinib trough concentration from 3-month treatment.

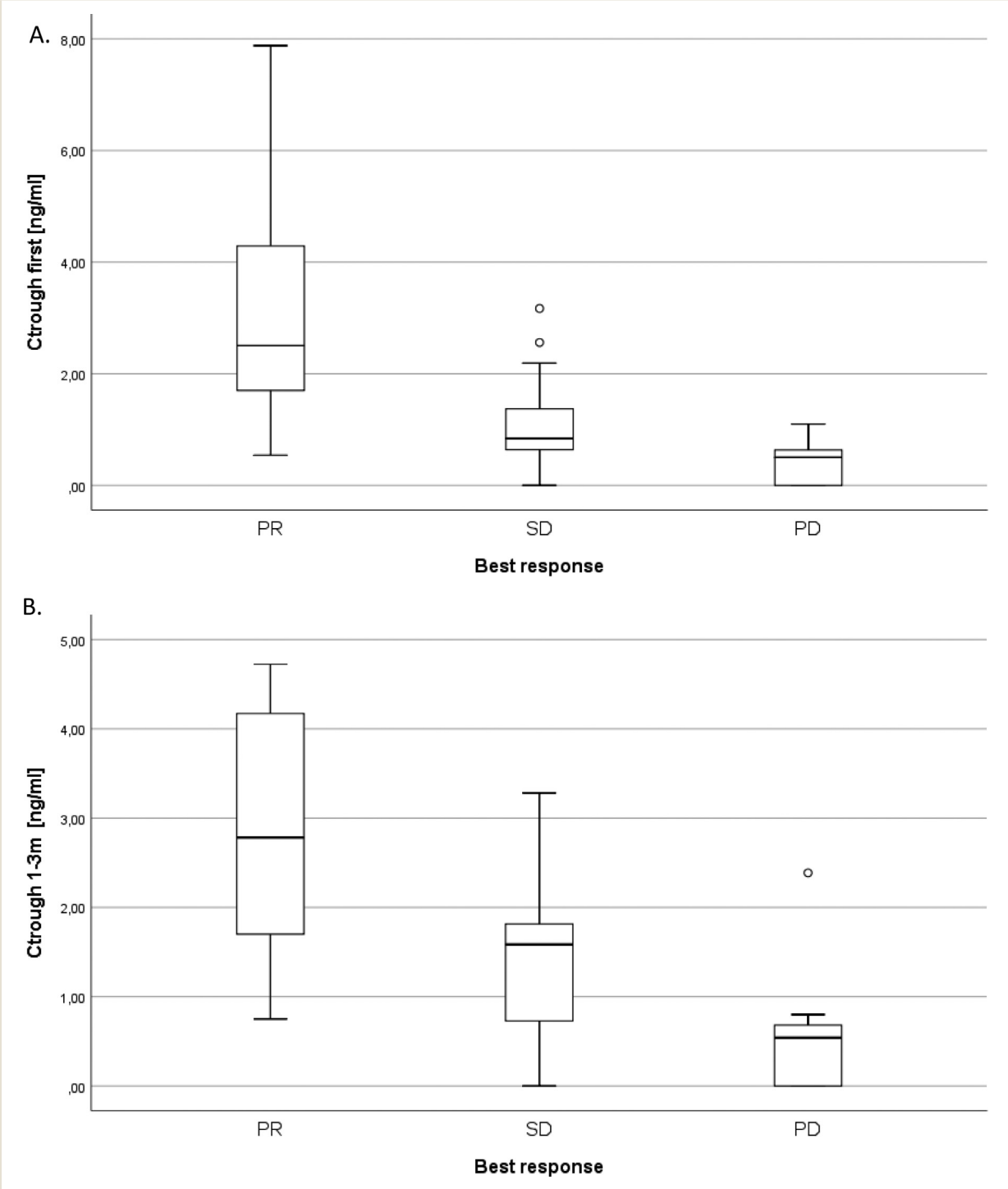

Table 3 Best Response and Trough Concentration of Axitinib

Median C_{trough} (ng/mL)	Best response			*P-value*
	PR (n = 6)	SD (n = 17)	PD (n = 11)	
$C_{trough\ first}$	2.51	0.84	0.5	**.004**
	Post hoc analysis: PD-SD: P = 0.072; **PD-PR: P = .004;** SD-PR: P = .349			
$C_{trough\ 1\text{-}3\ m}$	2.78	1.59	0.54	**.008**
	Post hoc analysis: **PD-SD: P = .049; PD-PR: P = .011;** SD-PR: P = .731			

PR, partial response; SD, steable disease; PD, progression disease; n, number of patients.

Table 4 Axitinib Trough Concentration and PFS, OS, and ≥ G3 Toxicity

Mean axitinib concentration (ng/mL)			*P-value*
	PFS < 5 mo	**PFS ≥ 5 mo**	
$C_{trough\ first}$ (12 vs. 22)	0.52	1.24	**.003**
$C_{trough\ 1\text{-}3m}$ (12 vs. 22)	0.57	1.76	**.001**
	OS < 25 mo	**OS ≥ 25 mo**	
$C_{trough\ first}$ (16 vs. 18)	0.59	1.00	.142
$C_{trough\ 1\text{-}3m}$ (16 vs. 18)	0.64	1.64	.097
	AEs < G3	**AEs ≥ G3**	
$C_{trough\ first}$ (31 vs. 3)	0.73	3.17	**.012**
$C_{trough\ 1\text{-}3m}$ (23 vs. 11)	0.73	2.50	**.003**

$C_{trough\ first}$, first axitinib trough concentration measurement; $C_{trough\ 1\text{-}3m}$, mean axitinib trough concentration measured through 3 months of treatment; PFS, progression-free survival; OS, overall survival; AEs, adverse events.

Discussion

Tyrosine kinase inhibitors are administered at strictly fixed doses regardless of body weight. There are data regarding interpatient variability of axitinib exposure, expressed by the AUC value, in the group of patients receiving a standard starting dose of 5 mg BID.[14] Due to this, the same dose may result in lower concentrations and less effective treatment in certain patients on one hand, while too high concentrations may pose a risk of unacceptable toxicity on the other hand.[9]

A significant association between the C_{trough} value and the best treatment response, PFS and toxicity severity was observed. Therefore, a C_{trough} measurement appears to be a valuable method to use for monitoring of axitinib therapy. To date, the values for therapeutic monitoring of this drug have been determined based on the AUC.[10] In the analysis of phase II studies, a 1.5-fold higher potential for achieving partial response with the increase in the AUC by 100 h*ng/mL and a statistically significant difference in mPFS and mOS depending on the AUC < 300 and ≥ 300 h*ng/mL have been demonstrated.[4] The AUC value of > 300 h*ng/mL is reported in article describing recommendations for the monitoring of molecularly targeted therapies.[5,9] In another article (Beinse et al.), therapy monitoring was based on the C_{max} value. The authors chose this method due to a short axitinib half-life.[15] Japanese researchers determined a proposed concentration range for C_{max}: 12.4-40.2 ng/mL.[16] However, it should be noted that the optimum time for blood collection in the method based on C_{max} values is difficult to determine.

In addition, the authors of publications indicate that therapy monitoring based on the AUC is difficult to apply in practice and uncomfortable for a patient as it requires the collection of a few blood samples after a single dose, while a more practical method involves the C_{trough} values.[5] To date, C_{trough} ≥ 5 ng/mL described by Tsuchiya et al. has not been confirmed in other studies. Moreover, the study only showed a tendency to longer PFS without statistically significant relationships.[6]

The C_{trough} values in the study group were lower than those reported by the Japanese investigators. Possible reasons may be ethnic differences. Although there were no significant differences in axitinib pharmacokinetics reported in the meta-analysis of ethnic differences, a higher variability level regarding steady-state $AUC_{0\text{-}24}$ and C_{max} values was observed in the Japanese group.[12] Rini et al. described 25% lower axitinib clearance values in the Japanese population resulting in 25% higher blood levels of the drug.[4] In addition, higher AUC_{12} values (292.1 h*ng/mL) compared to the values reported in the worldwide literature (130.5-187.5 h*ng/mL) were observed in another study in the Japanese population.[11]

Another important aspect is the monitoring of concentrations during the later phase of treatment. Maintaining the therapeutic drug concentrations throughout the overall treatment period also appears to be vital in cancer therapy; therefore, a single measurement may not be sufficient for assessment. In addition to significant differences (not for OS) for a single measurement, mean values from 3-month observation were also evaluated. A large intrapatient variability of blood levels of the drug may affect the reliability of a single measurement concerning assessment of the therapeutic drug blood concentration, as indicated by Arasatnam et al.[13] Significant results for mean values from 3-month

observation might be used to determine indications for therapy monitoring over a longer period. Therapy of advanced cancer is known to be provided until disease progression or unacceptable toxicity are observed (frequently for many months).

Currently, the relevant interest is focused on searching for possible predictive factors for combining treatment of TKI with checkpoint inhibitors. To date, there are no predictive factors for the treatment of aRCC. The only factors used in making clinical decisions are still MSKCC and IMDC scales.[17]

There are many factors that influence the response to the treatment with axitinib including VEGFR resistance.[18] Moreover, the response mechanisms to combination therapy with checkpoint inhibitors seems to be more complex, as described Argentiero et al.[17]

It is essential to take into consideration the fact that the concentration of the drug should not be the only factor influencing the treatment choice. However, taking together clinical factors, and drug concentration could be helpful in making decisions about dose changes or breaks during the treatment. There is still a place for axitinib monotherapy in second or further lines of the therapy for selected patients, especially for those treated with TKI in first-line,[19] and such relationships between the drug concentration and treatment efficacy and toxicity can significantly influence the clinical decisions during the therapy.

Conclusion

Statistically significant relationships between the axitinib C_{trough} value and treatment response, PFS and at least grade 3 toxicity were observed. Considering such vital relationships, it is worth taking measures to optimize the treatment of patients with renal cell carcinoma. C_{trough}-based therapy monitoring may be a valuable tool to improve the efficacy, and safety of axitinib treatment. However, it should not be a sole tool for treatment decisions because of the advanced mechanisms involved in the development of mRCC. Further studies are required to determine therapeutic concentrations for axitinib therapy monitoring and its utility, especially in the combining treatment (considering combined treatment with checkpoint inhibitors).

Clinical Practise Point

- Tyrosine kinase inhibitors are administered at strictly fixed doses. On the one hand it may result in lower concentrations and less effective treatment in certain patients, while too high concentrations may pose a risk of unacceptable toxicity on the other hand. There are data regarding interpatient variability of axitinib exposure, expressed by the area under the curve (AUC) value, in the group of patients receiving a standard starting dose of 5 mg BID.
- To date, correlations between axitinib exposure, and therapy efficacy have been evaluated mainly based on the AUC values. However, this method in not convenient for patients because it requires multiple blood sampling. The measurement of axitinib trough concentration (C_{trough}) seems more practical because it usually requires only 1 blood sample. To date, no reports assessing a relationship between axitinib C_{trough} and treatment efficacy and toxicity are available except the article presented by Tsuchiya et al.
- We found a significant relationship between measured axitinib C_{trough} value and treatment response, median progression-free survival and toxicity in the group of 35 patients. The data collected may be used to determine indications for axitinib therapy monitoring based on C_{trough} measurements.
- Axitinib is currently recommended for the first line treatment of advanced renal-cell carcinoma in combination with check-point inhibitors pembrolizumab or avelumab. Moreover, it is still an option for second-line therapy. The measurement of axitinib C_{trough} could have an impact on the improvement of treatment efficacy and safety.

Disclosure

The authors have stated that they have no conflicts of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

I would like to thank all patients and medical staff who contributed to the study.

CRediT authorship contribution statement

Zuzanna Synowiec: Conceptualization, Data curation, Investigation, Formal analysis, Writing – original draft, Writing – review & editing. **Katarzyna Sobańska:** Validation, Data curation, Formal analysis. **Tomasz Synowiec:** Software, Writing – review & editing. **Artur Teżyk:** Methodology, Validation. **Piotr Tomczak:** Conceptualization, Supervision. **Anna Jabłecka:** Conceptualization, Supervision, Writing – review & editing.

References

1. Motzer RJ, Escudier B, Tomczak P, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. *Lancet Oncol.* 2013;14:552–562. doi:10.1016/S1470-2045(13)70093-7.

2. Rini BI, Plimack E, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2019;380:1116–1127. doi:10.1056/NEJMoa1816714.
3. Motzer R, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2019;380:1103–1115. doi:10.1056/NEJMoa1816047.
4. Rini BI, Garrett M, Poland B, et al. Axitinib in metastatic renal cell carcinoma: results of a pharmacokinetic and pharmacodynamic analysis. *J Clin Pharmacol*. 2013;53:491–504. doi:10.1002/jcph.73.
5. Verheijen RB, Yu H, Schellens JHM, et al. Practical recommendations for therapeutic drug monitoring of kinase inhibitors in oncology. *Clin Pharmacol Ther*. 2017 Nov;102:765–776. doi:10.1002/cpt.787.
6. Tsuchiya N, Igarashi R, Suzuki-Honma N, et al. Association of pharmacokinetics of axitinib with treatment outcome and adverse events in advanced renal cell carcinoma patients. *J Clin Oncol*. 2015(suppl 7):506 abstr. doi:10.1200/jco.2015.33.7_suppl.506.
7. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228–247. doi:10.1016/j.ejca.2008.10.026.
8. Common terminology criteria for adverse events Accessed from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.html accessed date 18 Feb 2022.
9. Groenland SL, Mathijssen RHJ, Beijnen JH, et al. Individualized dosing of oral targeted therapies in oncology is crucial in the era of precision medicine. *Eur J Clin Pharmacol*. 2019;75:1309–1318. doi:10.1007/s00228-019-02704-2.
10. Yu H, Steeghs N, Nijenhuis CM, et al. Practical guidelines for therapeutic drug monitoring of anticancer tyrosine kinase inhibitors: focus on the pharmacokinetic targets. *Clin Pharmacokinet*. 2014;53:305–325. doi:10.1007/s40262-014-0137-2.
11. Miura Y, Imamura CK, Uchino K, et al. Individualized dosing of axitinib based on first-dose area under the concentration-time curve for metastatic renal-cell carcinoma. *Clin Genitourin Cancer*. 2019;17:e1–e11. doi:10.1016/j.clgc.2018.09.015.
12. Chen Y, Suzuki A, Tortorici MA, et al. Axitinib plasma pharmacokinetics and ethic differences. *Invest New Drugs*. 2015;33:521–532. doi:10.1007/s10637-015-0214-x.
13. Arasaratnam M, Crumbaker M, Bhatnagar A, et al. Inter- and intra-patient variability in pharmacokinetics of abiraterone acetate in metastatic prostate cancer. *Cancer Chemother Pharmacol*. 2019;84:139–146. doi:10.1007/s00280-019-03862-x.
14. Schmidinger M, Danesi R, Jones R, et al. Individualized dosing with axitinib: rationale and practical guidance. *Future Oncol*. 2018;14:861–875. doi:10.2217/fon-2017-0455.
15. Beinse G, Hulin A, Rousseau B. Axitinib pharmacologic therapeutic monitoring reveals severe under-exposure despite titration in patients with metastatic renal cell carcinoma. *Invest New Drugs*. 2019;37:1289–1291. doi:10.1007/s10637-019-00743-1.
16. Fukudo M, Tamaki G, Azumi M, et al. Absorption of the orally active multikinase inhibitor axitinib as a therapeutic index to guide dose titration in metastatic renal cell carcinoma. *Invest New Drugs*. 2020. doi:10.1007/s10637-020-01023-z.
17. Argentiero A, Solimando AG, Krebs M, et al. Anti-angiogenesis and immunotherapy: novel paradigms to envision tailored approaches in renal cell-carcinoma. *J Clin Med*. 2020;9:1594. doi:10.3390/jcm9051594.
18. Rini BI, Melichar B, Ueda T, et al. Axitinib with or without dose titration for first-line metastatic renal-cell carcinoma: a randomised double-blind phase 2 trial. *Lancet Oncol*. 2013;14:1233–1242. doi:10.1016/S1470-2045(13)70464-9.
19. Escudier BC, Porta C, Schmidinger M, et al. Renal cell carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2019;30:706–720. doi:10.1093/annonc/mdz056.