Axitinib dose titration: analyses of exposure, blood pressure and clinical response from a randomized phase II study in metastatic renal cell carcinoma

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Background: In a randomized, double-blind phase II trial in patients with metastatic renal cell carcinoma (mRCC), axitinib versus placebo titration yielded a significantly higher objective response rate. We evaluated pharmacokinetic and blood pressure (BP) data from this study to elucidate relationships among axitinib exposure, BP change, and efficacy.

Patients and methods: Patients received axitinib 5 mg twice daily during a lead-in period. Patients who met dose-titration criteria were randomized 1:1 to stepwise dose increases with axitinib or placebo. Patients ineligible for randomization continued without dose increases. Serial 6-h and sparse pharmacokinetic sampling were carried out; BP was measured at clinic visits and at home in all patients, and by 24-h ambulatory BP monitoring (ABPM) in a subset of patients.

Results: Area under the plasma concentration–time curve from 0 to 24 h throughout the course of treatment (AUCstudy) was higher in patients with complete or partial responses than those with stable or progressive disease in the axitinib-titration arm, but comparable between these groups in the placebo-titration and nonrandomized arms. In the overall population, AUCstudy and efficacy outcomes were not strongly correlated. Mean BP across the population was similar when measured in clinic, at home, or by 24-h ABPM. Weak correlations were observed between axitinib steady-state exposure and diastolic BP. When grouped by change in diastolic BP from baseline, patients in the ≥10 and ≥15 mmHg groups had longer progression-free survival.

Conclusions: Optimal axitinib exposure may differ among patients with mRCC. Pharmacokinetic or BP measurements cannot be used exclusively to guide axitinib dosing. Individualization of treatment with vascular endothelial growth factor receptor tyrosine kinase inhibitors, including axitinib, is thus more complex than anticipated and cannot be limited to a single clinical factor.

Key words: axitinib, renal cell carcinoma, dose titration, pharmacokinetics, blood pressure

Introduction
Axitinib, a potent, selective tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor (VEGF) receptors (VEGFR) [1], is approved globally for second-line treatment of advanced renal cell carcinoma (RCC) [2]. Similar to observations with other oral drugs, including VEGFR TKIs [3–5], patients treated with axitinib exhibit variable plasma exposure [6]. Retrospective analyses using pooled data from phase II studies of axitinib in previously treated patients with metastatic RCC (mRCC) showed that higher drug exposure and increases in diastolic blood pressure (dBP), a recognized class effect of antiangiogenic agents [7], correlated with improved outcomes [8]. Moreover, patients titrated above the 5-mg twice daily (b.i.d.) axitinib starting dose had lower drug exposure at 5 mg b.i.d. than patients who did not increase axitinib dosage [9], and titration to 7 or 10 mg b.i.d. yielded axitinib exposure comparable to patients who remained on 5 mg b.i.d. These data suggested that upward dose titration based on individual tolerability generally increases axitinib exposure, and axitinib dose increases have the potential to improve efficacy in patients with sub-optimal plasma drug exposure at the starting dose.
In a prospective, randomized, double-blind phase II trial in patients with previously untreated mRCC, patients receiving axitinib dose titration demonstrated a significantly higher objective response rate (ORR) versus those receiving placebo titration (54% versus 34%; one-sided \( P = 0.019 \)) [10]. The progression-free survival (PFS) hazard ratio (HR) 0.85 [95% confidence interval (CI) 0.54–1.35] favoring axitinib titration was not statistically significant (one-sided stratified \( P = 0.24 \)). Although the study was not powered to detect differences in PFS, the discrepancy between ORR and PFS may have been in the study was not powered to detect differences in PFS, the discrepancy between ORR and PFS may have been influenced by the higher proportion of dose reductions after upward titration in the axitinib-titration arm. This finding suggested that both identification of patients who may benefit from dose titration and optimization of axitinib exposure in these patients require further refinement, for instance, by employing pharmacokinetic parameters or other clinical criteria in the decision to titrate the axitinib dose.

We assessed pharmacokinetic and BP data collected in this axitinib dose-titration trial to elucidate relationships among axitinib exposure, BP, and clinical outcomes and provide suggestions to improve the dose-titration strategy.

**methods**

**study design**

Key eligibility criteria were previously described ([10] and supplementary Text, available at Annals of Oncology online). Axitinib was administered orally in 4-week cycles, continuously. All patients received axitinib 5 mg b.i.d. during cycle 1 (lead-in period). After cycle 1, patients were randomized 1:1 to axitinib- or placebo-titration if they met the following criteria over two consecutive weeks: BP ≤ 150/90 mmHg, no grade 3/4 axitinib-related toxicities, no dose reduction, and use of no more than two concurrent antihypertensive medications. Patients were stratified by Eastern Cooperative Oncology Group performance status ECOG PS (0 versus 1) at the time of randomization.

Randomized patients had the dose titrated stepwise to 7 mg b.i.d. (5 mg axitinib + 2 mg axitinib or placebo), and then to a maximum of 10 mg b.i.d. (5 mg axitinib + 5 mg axitinib or placebo) if the above criteria were met for two additional consecutive weeks [10]. Patients and investigators were blinded to axitinib versus placebo dose titration. Patients not meeting the randomization criteria after cycle 1 continued to receive axitinib 5 mg b.i.d. Axitinib dose reductions based on tolerability were allowed in all arms [10]. The trial was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization guidelines on Good Clinical Practice, and applicable local regulatory requirements and laws. All patients provided written informed consent. The protocol and informed consent forms were approved by an institutional review board or independent ethics committee at each study center. This trial is registered on ClinicalTrials.gov (NCT00835978).

**pharmacokinetic–pharmacodynamic analyses**

Serial 6-h pharmacokinetic sampling (0, 0.5, 1, 2, 4, and 6 h post-dose) was carried out in a subset of patients on cycle-1/day-15 (target of 75) and cycle-2/day-15 (target of 24 in randomized arms) (supplementary Figure S1, available at Annals of Oncology online). Sparse pharmacokinetic sampling (0 and 2 h post-dose) was carried out in remaining patients on cycle-1/day-15, and in randomized arms only, on cycle-2/day-15 and ≥4 days after titration to 10 mg b.i.d. Plasma axitinib concentrations were determined using a validated high-performance liquid chromatography with tandem mass-spectrometry method [6].

Blood pressure was measured at clinic visits and at home in all patients, and additionally by 24-h ambulatory BP monitoring (ABPM) in the same group of patients from whom serial 6-h pharmacokinetic sampling was drawn (supplementary Text and Figure S1, available at Annals of Oncology online). For exploratory analyses of the relationship between axitinib exposure and clinical outcomes, mean area under the plasma concentration–time curve from 0 to 24 h (AUC_{0-24}) before randomization (AUC_{cycle1}) and throughout the entire course of axitinib treatment (AUC_{cycle}) were derived using dosing information and individual post-hoc clearance estimates, using serial 6-h and sparse pharmacokinetic data based on a previous pharmacokinetic model [8].

For post-hoc exploratory analyses of the relationship between BP and PFS, patients were based on the basis of in-clinic BP measurements during axitinib treatment (change from baseline in dBP ≥ 10 versus <10 mmHg and ≥15 versus <15 mmHg). In addition, landmark analyses were conducted using the maximum dBP achieved by 9 weeks of treatment (to allow for three in-clinic BP measurements and two stepwise dose increases in the randomized arms) to group patients, and PFS was assessed from that point forward. Time-to-event analyses in AUC_{cycle1} and BP groups were conducted with Cox proportional hazards regression models using S-PLUS® v7.0 (Insightful Corp., Seattle, WA) and SAS® v9.2 (SAS Institute Inc, Cary, NC), respectively, and plotted with Kaplan–Meier survival curves. One-sided unstratified log-rank tests were used to compare PFS between BP groups.

Correlations of mean change in BP from baseline or mean absolute BP measurements and axitinib pharmacokinetics (derived from axitinib concentration–time data and estimated by noncompartmental methods) were assessed in patients with matched serial pharmacokinetic and ABPM data on cycle-1/day-15.

**statistical analysis**

Results for the primary end point, ORR in the axitinib- versus placebo-titration arms, are published [10]. Secondary end points included pharmacokinetic and BP measurements. The study was not powered to detect differences in axitinib pharmacokinetics among treatment arms. Statistical analyses were conducted using SAS v9.2.

**results**

**patients, treatment, and pharmacokinetic and BP measurements**

As previously reported [10], of 213 patients, 112 were eligible for dose titration following the lead-in period and 56 patients each were randomized to axitinib or placebo titration; 91 patients were ineligible for dose titration (nonrandomized arm), and 10 withdrew during the lead-in period. In the overall population, the median age was 62 years, 67% were male, 64% had ECOG PS 0, and 86% had prior nephrectomy [10]. The median daily axitinib dose (range) was 13.5 mg (5.2–19.5), 10.0 mg (6.8–10.0), and 9.3 mg (3.9–10.4) in the axitinib-titration, placebo-titration, and nonrandomized arms, respectively.

Population pharmacokinetic analysis using both serial and sparse concentration data showed lower mean \( AUC_{cycle1} \) at the axitinib 5-mg b.i.d. starting dose in patients eligible for dose titration compared with those not eligible (supplementary Text, available at Annals of Oncology online). Mean \( AUC_{cycle1} \) increased in the axitinib- but not the placebo-titration arm, and decreased in nonrandomized patients.
Based on 24-h ABPM, mean BP reached near maximal values by day 4 of axitinib treatment, with little additional increase by day 15 (supplementary Table S1 and Figure S2, available at Annals of Oncology online). The BP profile on all assessment days followed typical diurnal variation patterns, with change from baseline on days 4 and 15 generally consistent at all clock times. Mean dBP at baseline was similar when measured in clinic (75.9 mmHg), at home (76.5 mmHg), or by 24-h ABPM (73.1 mmHg). On cycle-1/day-15, mean dBP was also comparable by clinic (84.2 mmHg), home (84.1 mmHg), and 24-h ABPM (84.7 mmHg) measurements. Similar systolic BP outcomes were also observed across various time points and measurement modalities (supplementary Text and Figure S3, available at Annals of Oncology online).

relationship between axitinib exposure and efficacy

Axitinib exposure (AUC_{study}) was higher in patients with complete or partial responses than in those with stable or progressive disease in the axitinib-titration arm, but comparable between patients in different Response Evaluation Criteria in Solid Tumors categories (Supplementary Text, available at Annals of Oncology online) in the placebo-titration and nonrandomized arms (Figure 1).

Efficacy outcomes were similar in patients with AUC_{study} greater than or equal to the median (261 ng·h/ml; n = 83) and those with AUC_{study} less than the median (n = 84) ORR 51% versus 45%; median PFS (mPFS) 13.0 versus 16.5 months (HR 1.00; 95% CI 0.69–1.47; P = 0.981). When other AUC_{study} thresholds were evaluated (data not shown), the largest difference in ORR and HR for PFS was observed in patients with AUC_{study} ≥ 200 (n = 118) versus <200 ng·h/ml (n = 49): ORR 53% versus 37%; mPFS 13.9 versus 11.5 months (HR 0.83; 95% CI 0.55–1.24; P = 0.355). The difference in PFS between patients with AUC_{study} ≥ 200 versus <200 ng·h/ml was greater in the axitinib-titration versus placebo-titration or non-randomized arms (Figure 2B–D).

When grouped by AUC_{study} quartiles (Figure 3), patients in quartile 2 (191–260 ng·h/ml) exhibited a trend of longer mPFS (19.4 months) compared with other quartiles (range 11.5–13.9 months).

relationship between BP and efficacy

Longer PFS was observed in patients with dBP change from baseline ≥10 (n = 176) versus <10 mmHg (n = 27) (median: 16.6 versus 5.7 months; HR 0.40; 95% CI 0.25–0.65; one-sided P < 0.001), and in patients with change ≥15 (n = 144) versus <15 mmHg (n = 59) (median: 16.6 versus 9.2 months; HR 0.70; 95% CI 0.48–1.02; one-sided P = 0.031). In landmark analyses, smaller differences in PFS were observed between these groups (data not shown).

relationship between axitinib exposure and ambulatory BP

On cycle-1/day-15, mean AUC_{24} and maximum observed plasma concentration were higher in patients with mean dBP change from baseline ≥15 versus <15 mmHg (Figure 4A and B). Similarly, higher axitinib exposure was observed in patients with mean dBP ≥90 versus <90 mmHg (data not shown). When dBP was plotted as a continuous variable, a weak correlation (R^2 = 0.225) was observed between axitinib plasma steady-state exposure and mean change from baseline in dBP on cycle-1/day-15 (Figure 4C). A similar observation was seen using mean absolute dBP on cycle-1/day-15 (R^2 = 0.126).

discussion

Selecting the appropriate dose of oral targeted agents remains a challenge in oncology trials. Primary results from the randomized

![Figure 1. AUC_{study} by best-observed RECIST response. Whiskers are drawn to the nearest value not beyond a standard span from the quartiles (1.5x inter-quartile range); outliers are drawn individually as dots overlaid by lines. AUC_{study}, area under the plasma concentration–time curve from 0 to 24 h throughout the course of treatment; CR, complete response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.](image-url)
phase II trial of axitinib with or without dose titration for first-line mRCC validated the practice of increasing axitinib doses according to individual tolerability [10]. The objective of the analyses reported here was to use pharmacokinetic and BP data collected during this study to delineate the relationships among axitinib exposure, BP, and efficacy, which may aid clinicians in developing strategies to enhance axitinib exposure in individual patients to achieve favorable clinical outcomes without undue toxicity.

This analysis showed that treatment-naive patients eligible for dose titration had lower plasma exposure at the 5-mg b.i.d. starting dose. Moreover, axitinib, but not placebo, dose titration increased drug exposure, reflected in the higher ORR and PFS (albeit not statistically significant for PFS) [10]. Interestingly, associations between drug exposure and clinical end points were seen in axitinib-titrated patients only, suggesting that below a certain threshold (e.g., 5 mg b.i.d.), efficacy is determined by other individual factors yet to be identified. As previously suggested [10], there does not appear to be a uniform, optimal drug exposure target that may be applied across all patients. Given

![Figure 2](image-url)  
**Figure 2.** Kaplan–Meier plot of PFS in patients with AUC\textsubscript{study} ≥ 200 versus <200 ng·h/ml in the (A) overall population, (B) axitinib-titration arm, (C) placebo-titration arm and (D) nonrandomized arm. AUC\textsubscript{study}, area under the plasma concentration–time curve from 0 to 24 h throughout the course of treatment; CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival.

![Figure 3](image-url)  
**Figure 3.** Kaplan–Meier plot of PFS in patients grouped into quartiles by AUC\textsubscript{study}. AUC\textsubscript{study}, area under the plasma concentration–time curve from 0 to 24 h throughout the course of treatment; CI, confidence interval; NE, not estimable; PFS, progression-free survival; Q, quartile.
the expected variations among axitinib-treated patients, as well as the short plasma half-life of axitinib [2, 6] and lack of a defined timeframe during which drug concentrations are most predictive of overall exposure, scheduled pharmacokinetic measurements in individual patients for the purpose of guiding axitinib dosing are not justified at this time.

Patients who developed increased BP during axitinib treatment appeared to have longer PFS than those who did not. Smaller differences in PFS were observed by landmark analyses, presumably because patients who die or experience disease progression before the landmark (17% in the present analysis) are excluded. Nevertheless, in the absence of a strong association between BP and plasma exposure in individual patients, BP elevation should not be used as the exclusive tool to manage axitinib dosing. This is consistent with the current axitinib titration guidelines [2], which take into account grade >2 adverse events and antihypertensive medication use along with BP measurements. Of note, the intent of axitinib dose titration is not to drive all patients into a hypertensive state. Rather, it is recognized that an increase in BP after treatment with axitinib or other VEGFR TKIs may be a predictor of better response [8]. Monitoring BP is an important component of the management of patients treated with anti-VEGF agents, given the frequent occurrence of hypertension [7]. The present trial may be among the first to provide prospective data comparing different modes of BP monitoring during VEGFR TKI therapy. Because axitinib trials require daily BP monitoring as well as management of BP exceeding protocol-defined thresholds, hypertension-related sequelae are uncommon [11]. Antihypertensive medication use was not evaluated here. However, based on analyses in axitinib-
treated patients with advanced solid tumors [12], it is not expected that administration of these drugs at baseline or during therapy would compromise efficacy.

The current analyses have obvious limitations as they are post hoc and exploratory. The pooled analysis of exposure and efficacy may have been confounded by active dose-titration in only the axitinib-titration arm, whereas the analysis of BP and efficacy may have been prone to bias due to post-randomization events (e.g. dose increases allowed in the axitinib-titration arm in patients who tolerated the drug and did not register a major increase in BP to >150/90 mmHg following initial treatment). Moreover, stepwise axitinib b.i.d. titration did not allow for smaller refinements in axitinib dosing, which may have allowed some titrated patients to maintain a higher dose for a longer period without compromising tolerability. Likewise, following up titration, dose decreases to below the starting dose (5 mg b.i.d.), reported in 18% of patients in the axitinib-titration arm [10], might have confounded the efficacy results. Investigator bias or variability in selection of patients eligible for randomization to dose titration as well as in modification of doses due to adverse events following titration may have also influenced the data reported here, making the groups less uniform than planned. In addition, the study was not powered to detect pharmacokinetic differences among or within treatment arms, and the post-hoc analyses were not powered to compare BP groups.

In conclusion, the data presented here indicate pharmacokinetic or BP measurements cannot be used exclusively to guide axitinib dosing. Individualization of treatment with VEGFR TKIs, including axitinib, is thus more complex than anticipated and cannot be limited to a single clinical factor. The current axitinib dose-titration scheme, based on individual patient tolerability, allows the majority of patients who are likely obtaining lower plasma exposures at the starting dose to increase drug levels, offering one method to personalize therapy. However, the results presented here show that neither clinical response nor BP increase is driven solely by drug exposure, and it may be overly simplistic to presume that increased exposure alone will guarantee improved outcomes. Pharmacodynamic and other factors may contribute to clinical response in an individual patient. Identification of pretreatment predictors of response in patients with RCC and investigation of other algorithms for dose titration, including based on radiographic response observed or use of intermediate doses (e.g. 6 mg b.i.d.), may help to optimize axitinib therapy [10].

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disclosure

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references