Individualised axitinib regimen for patients with metastatic renal cell carcinoma after treatment with checkpoint inhibitors: a multicentre, single-arm, phase 2 study

Moshe C Ornstein, Sumanta K Pal, Laura S Wood, Jackie M Tomer, Brian P Hobbs, Xuefei S Jia, Kimberly D Allman, Allison Martin, Thomas Olencki, Nancy B Davis, Timothy D Gilligan, Amir Mortazavi, W Kimryn Rathmell, Jorge A Garcia, Brian I Rini

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See Comment page 1332

Department of Hematology and Medical Oncology, Cleveland Clinic—Taussig Cancer Institute, Cleveland, OH, USA (M C Ornstein MD, L S Wood RN, J M Tomer MPH, B P Hobbs PhD, X S Jia MS, K D Allman CNP, A Martin PA-C, T D Gilligan MD, J A Garcia MD, Prof B I Rini MD); **Department of Medical Oncology and Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, CA, USA** (S K Pal MD); **Division of Medical Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA** (Prof T Olencki DO, A Mortazavi MD); **and Division of Hematology and Oncology, Vanderbilt Ingram Cancer Center, Nashville, TN, USA** (N B Davis MD, Prof W K Rathmell MD)

Correspondence to:
Dr Moshe C Ornstein, Cleveland Clinic—Taussig Cancer Institute, Cleveland, OH 44195, USA
ornstem@ccf.org

Summary

Background Checkpoint inhibitor therapy is a standard of care for patients with metastatic renal cell carcinoma. Treatment options after checkpoint inhibitor therapy include vascular endothelial growth factor receptor (VEGF-R) tyrosine kinase inhibitors, although no prospective data regarding their use in this setting exist. Axitinib is a VEGF-R inhibitor with clinical data supporting increased activity with dose titration. We aimed to investigate the activity of dose titrated axitinib in patients with metastatic renal cell carcinoma who were previously treated with checkpoint inhibitor.

Methods We did a multicentre, phase 2 trial of axitinib given on an individualised dosing algorithm. Patients at least 18 years of age with histologically or cytologically confirmed locally recurrent or metastatic renal cell carcinoma with clear cell histology, a Karnofsky Performance Status of 70% or more, and measurable disease who received checkpoint inhibitor therapy as the most recent treatment were eligible. There was no limit on number of previous therapies received. Patients received oral axitinib at a starting dose of 5 mg twice daily with dose titration every 14 days in 1 mg increments (ie, 5 mg twice daily to 6 mg twice daily, up to 10 mg twice daily maximum dose) if there was no axitinib-related grade 2 or higher mucositis, diarrhoea, hand-foot syndrome, or fatigue. If one or more of these grade 2 adverse events occurred, axitinib was withheld for 3 days before the same dose was resumed. Dose reductions were made if recurrent grade 2 adverse events despite treatment breaks or grade 3–4 adverse events occurred. The primary outcome was progression-free survival. Analyses were done per protocol in all patients who received at least one dose of axitinib. Recruitment has been completed and the trial is ongoing. This trial is registered with ClincalTrials.gov, number NCT02579811.

Findings Between Jan 5, 2016 and Feb 21, 2018, 40 patients were enrolled and received at least one dose of study treatment. With a median follow-up of 8·7 months (IQR 3·7–14·2), the median progression-free survival was 8·8 months (95% CI 5·7–16·6). Fatigue (83%) and hypertension (75%) were the most common all-grade adverse events. The most common grade 3 adverse event was hypertension (24 patients [60%]). There was one (3%) grade 4 adverse event (elevated lipase) and no treatment-related deaths occurred. Serious adverse events that were likely related to therapy occurred in eight (20%) patients; the most common were dehydration (n=4) and diarrhoea (n=2).

Interpretation Individualised axitinib dosing in patients with metastatic renal cell inoma previously treated with checkpoint inhibitors did not meet the prespecified threshold for progression free survival, but these data show that this individualised titration scheme is feasible and has robust clinical activity. These prospective results warrant consideration of axitinib in this setting.

Funding Pfizer.

Introduction

Immune checkpoint inhibitor therapy is a standard of care for patients with metastatic renal cell carcinoma. The combination of ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) is approved for patients with treatment-naive, intermediate-risk and poor-risk metastatic renal cell carcinoma, and nivolumab monotherapy is approved for previously treated patients with metastatic renal cell carcinoma.[1,2] A commonly used treatment option after checkpoint inhibitor therapy is vascular endothelial growth factor receptor (VEGF-R) tyrosine kinase inhibitors.[3–6] There is retrospective data[3–12] support VEGF-R tyrosine kinase inhibitor therapy after checkpoint inhibitor use in patients with metastatic renal cell carcinoma; however, to our knowledge, no prospective data exist in this population to date.

Axitinib is a potent VEGF-R tyrosine kinase inhibitor that selectively targets VEGF-R 1, 2, and 3 and is approved for the treatment of previously treated metastatic renal cell carcinoma.[13] It was approved on the basis of superior progression-free survival compared with the VEGF-R tyrosine kinase inhibitor sorafenib in

Research in context

Evidence before this study

We searched PubMed to retrieve data regarding the efficacy of targeted therapies following checkpoint inhibitors in metastatic renal cell carcinoma from Jan 1, 2000, to March 31, 2019. The research contained an extensive range of key terms, including "metastatic renal cell carcinoma", "immunotherapy", "checkpoint inhibitors", "targeted therapy", "VEGF therapy", "axitinib", and "subsequent therapy", and was restricted to English-language publications. The findings show clinical activity of targeted therapies after checkpoint inhibitors, but all data were limited to retrospective reviews. We then search PubMed using the terms "metastatic renal cell carcinoma" and "axitinib titration" from Jan 1, 2000, to March 31, 2019. The published data support the role of axitinib titration in metastatic renal cell carcinoma but do not define optimal dose titration strategies. Taken together, these findings suggest a need for both prospective trials of axitinib after checkpoint inhibitors and a more refined dosing titration scheme.

Added value of this study

To our knowledge, this is the first prospective trial of any therapy in metastatic renal cell carcinoma patients who have previously been treated with checkpoint inhibitor therapy. Additionally, the novel dosing scheme in this study provides a clinically relevant framework to guide optimal dosing of axitinib for metastatic renal cell carcinoma patients. The high clinical activity with low high-grade toxicity is a reflection of this and this regimen could be immediately translatable to clinical practice.

Implications of all the available evidence

Our prospective data build on the published retrospective data that support the clinical activity of axitinib in patients with metastatic renal cell carcinoma previously treated with checkpoint inhibitor therapy. This prospective data shows that individualised axitinib dosing is feasible in this setting and provides evidence for implementing a toxicity-based titration scheme to improve clinical outcomes in these patients.

previously treated metastatic renal cell carcinoma.[14] Similarly, although a phase 3 trial of axitinib versus sorafenib in patients with treatment-naive metastatic renal cell carcinoma did not meet its primary endpoint, it did show meaningful clinical activity, with 32% achieving an objective response and median progression-free survival of 10·1 months (95% CI 7·2–12·1).[15] A key consideration with axitinib is the dose-response relationship, with preclinical data showing the linear pharmacokinetics of axitinib, such that an increased dose results in higher plasma concentrations and subsequent increased activity.[16] In a randomised, double-blind, phase 2 clinical trial of patients with treatment-naive metastatic renal cell carcinoma randomly assigned to axitinib dose titration or placebo titration, the proportion of patients achieving an objective response was 20% higher in the axitinib dose titration group (54% [95% CI 40–67] *vs* 34% [22–48], p=0·019), although no difference in progression-free survival and overall survival was observed.[17,18]

Despite the improved clinical activity of axitinib in a cohort of patients with dose titration, individual patient dose titration on the basis of the US Food & Drug Administration (FDA)-approved label remains a clinical challenge. In the approved dose escalation from a starting dose of 5 mg twice daily to 7 mg twice daily and then 10 mg twice daily, patients receive 140% and 200% of the starting dose. This substantial incremental dose increase can result in unacceptable toxicity and subsequent dose reductions to subtherapeutic doses. Similarly, with the on-label dose reductions for axitinib to 3 mg twice daily and then 2 mg twice daily, patients receive 60% and 40% of the starting dose, which can result in underdosing and decreased activity.

Given the absence of prospective data and constrained axitinib dosing schemes, we aimed to investigate the activity of individualised axitinib dosing in patients with metastatic renal cell carcinoma following treatment with checkpoint inhibitors.

Methods

Study design and participants

We did a multicentre, phase 2 trial of axitinib given on an individualised dosing algorithm at four cancer centres in the USA. Patients at least 18 years of age with histologically or cytologically confirmed locally recurrent or metastatic renal cell carcinoma with clear cell histology were eligible. Other key inclusion criteria were Karnofsky Performance Status of 70% or more, adequate organ function, and evidence of measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Previous nephrectomy was not required. Patients were required to have received at least one previous systemic therapy for renal cell carcinoma, with checkpoint inhibitor therapy as the most recent treatment. Previous bevacizumab or VEGF-R tyrosine kinase inhibitor therapy was permitted either in combination with checkpoint inhibitor therapy or as monotherapy before checkpoint inhibitor therapy. Previous axitinib was not permitted in any setting either as monotherapy or in combination with checkpoint inhibitor therapy. Exclusion criteria included uncontrolled hypertension (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg despite optimal medical therapy), major vascular events, or uncontrolled central nervous system metastases. Full inclusion and exclusion criteria are provided in the appendix (p 27).

See Online for appendix

Patients were enrolled at Cleveland Clinic Taussig Cancer Institute (Cleveland, OH), The Ohio State

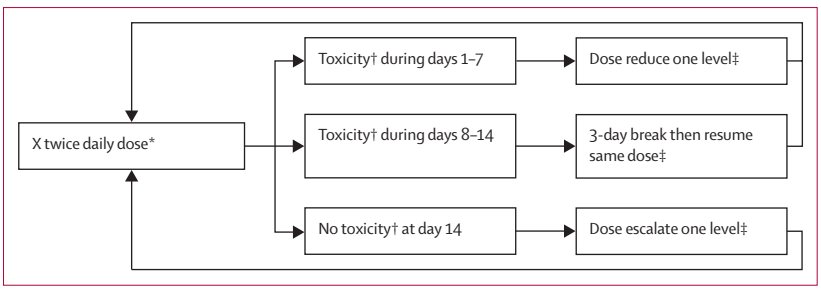

Figure 1: **Study scheme**
*Starting dose for all patients was 5 mg twice daily. †Dose modifications only for the following Grade 2 or higher toxicities: oral mucositis, diarrhoea, hand-foot syndrome, and fatigue. ‡Doses of 2–10 mg twice daily in 1 mg increments (ie, 5 mg twice daily to 6 mg twice daily, up to max dose of 10 mg twice daily, or 5 mg twice daily to 4 mg twice daily, down to minimum dose of 2 mg twice daily).

University Comprehensive Cancer Center (Columbus, OH), Vanderbilt Ingram Cancer Center (Nashville, TN), and City of Hope Comprehensive Cancer Center (Duarte, CA; appendix p 3). The institutional review boards of all participating institutions approved this study and the consent form. Written, informed consent was obtained from all patients.

Procedures

Patients were treated with a starting dose of axitinib of 5 mg twice daily taken orally. In the absence of grade 2 axitinib-related mucositis, diarrhoea, hand-foot syndrome, or fatigue, upward dose titration occurred every 14 days in 1 mg increments (ie, 5 mg twice daily to 6 mg twice daily, up to 10 mg twice daily max dose). Other toxicities (eg, controlled hypertension) were not explicitly considered in decisions regarding titration. If grade 2 adverse events occurred, therapy was suspended for 3 days, after which it was resumed at the same dose. Recurrent grade 2 adverse events despite treatment breaks or any grade 3–4 adverse events resulted in dose reduction in increments of 1 mg twice daily. This dosing scheme continued until a steady dose offering tolerability without recurrent grade 2 adverse events was identified (figure 1). Patients remained on therapy until disease progression or unacceptable toxicity.

Radiographic assessments at baseline included CT head, chest, abdomen, and pelvis and bone scans. Subsequent radiographic assessments included CT chest, abdomen, and pelvis scans every 8 weeks for the first 12 months and every 12 weeks thereafter. Brain and bone imaging was done after baseline per physician discretion as clinically indicated. Patients who achieved a partial response or complete response per RECIST version 1.1 had their tumour measurements confirmed by a non-treating physician at the respective institution, but not by central review. Standard blood work, including complete blood counts and comprehensive metabolic panels, was checked once per 28-day cycle.

Adverse events were monitored at clinic visit once per every 28-day cycle as well as once per week for the first two weeks after a dose change. Toxicities were graded per Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Outcomes

The primary outcome for this trial was progression-free survival, measured as the time between treatment start date and RECIST-defined disease progression or last follow-up date. Secondary outcomes were overall survival (not reported), the proportion of patients achieving an objective response, and adverse events. An additional secondary endpoint was assessment of anti-tumour effect in patients who underwent dose-escalation at the time of disease progression. However, this endpoint was not analysed because the study was designed for rapid early titration; thus, patients were generally at their maximum tolerated dose at disease progression, making further dose escalation not feasible.

Statistical analysis

At the time of study design, two retrospective reviews of patients treated with VEGF-R tyrosine kinase inhibitor following checkpoint inhibitor therapy for metastatic renal cell carcinoma showed median progression-free survival of approximately 6·5 months (6·4 months[3] and 6·6 months[4]). This study was designed to test the hypothesis that individualised toxicity-based dose titration would improve the clinical activity of axitinib with acceptable toxicity risk. Median progression-free survival assumed the null hypothesis value reported in the aforementioned retrospective reviews of 6·5 months. Assuming the single parameter exponential model for progression-free survival, sample size calculations targeted a 45% increase in median progression-free survival to 9·5 months, which would represent a clinically meaningful improvement. In the presence of 38 events, the one-sided log-rank test achieves power 0·80 with type I error controlled at 10%. Allowing for ineligible or unevaluable patients, the recruitment goal was set at 40 patients.

A proportion of 20% for axitinib discontinuation due to toxicity was considered unacceptable. If at any time more than two of ten, four of 20, or six of 30 patients had to discontinue due to toxicity, consideration would be given to stopping the study. All analyses were done per protocol in all patients who received at least one dose of axitinib. Patients were defined as non-assessable for response if they did not have follow-up imaging.

Progression-free survival was estimated using the Kaplan-Meier method with Greenwood's formula for interval estimation. The primary outcome was evaluated for statistical significance at the 0·05 level by comparing 95% CIs for median progression-free survival to the hypothesised null value. Student's *t* test and Fisher's exact test evaluated associations between objective response and checkpoint inhibitor therapy.

We did post-hoc analyses to evaluate event-free survival (defined as absence of an event at the 6-month and 12-month timepoints) and the effect of progression-free

survival in the subgroup of patients who discontinued previous immune checkpoint inhibitor therapy due to progressive disease.

p values of less than 0·05 were considered statistically significant. All statistical analyses were done using R version 3.5.0. The trial is registered at ClinicalTrials.gov, number NCT02579811.

Role of funding source

The funder of the study was involved in study design, but had no role in data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data and had final responsibility for the decision to submit for publication.

Results

Between Jan 5, 2016, and Feb 21, 2018, of 58 patients screened, 40 (69%) were enrolled (figure 2). All patients were eligible for and included in the final analysis. Patient characteristics are in table 1. Metastatic sites were typical for a metastatic renal cell carcinoma population (table 1). Most patients (29 [73%] of 40) received at least two previous systemic therapies for renal cell carcinoma (table 2). 28 (70%) of the 40 patients had received previous VEGF-directed therapy. The most common checkpoint inhibitor therapies patients had received were nivolumab monotherapy (25 [63%] of 40 patients) and the combination of ipilimumab and nivolumab (six [15%] of 40 patients; table 2).The majority of patients discontinued checkpoint inhibitor therapy owing to disease progression (37 [93%] of 40), with the remaining three patients discontinuing checkpoint inhibitor therapy owing to toxicity (one patient each: fatigue, pneumonitis, colitis; table 2). The median interval from checkpoint inhibitor discontinuation to treatment with axitinib was 1·1 months (IQR 0·7–1·7). The best previous response to checkpoint inhibitor therapy was partial response (eight [20%] of 40), stable disease (21 [53%] of 40), and progressive disease (ten [25%] of 40; table 2). The median duration on checkpoint inhibitor therapy was 4·8 months (IQR 2·0–8·7; table 2).

At data cutoff (Feb 14, 2019), the median follow-up 8·7 months (IQR 3·7–14·2). This trial did not meet its primary endpoint; median progression-free survival for all patients was 8·8 months (95% CI 5·7–16·6; figure 3). 18 (45%) of 40 patients achieved an objective response, with one (3%) achieving a complete response, 17 (43%) achieving a partial response, and 18 (45%) patients with stable disease as their best response. Four (10%) patients had progressive disease as best response. Of the 18 patients who responded to axitinib, 12 (67%) had a sustained response of more than 12 months. Most (14 [78%] of 18) patients who responded to therapy had previously received VEGF-directed therapy. At the time of follow-up data cutoff, ten (25%) of 40 patients were on therapy for a median duration of 15 months (IQR 13–24).

A post-hoc subgroup analysis showed a median progression-free survival for patients who discontinued checkpoint inhibitors due to progressive disease (n=37) was 9·2 months (95% CI 6·20–16·59). 6-month event-free survival was 63% (49–80) and 12-month event-free survival was 38% (25–56).

Four (36%) of 11 patients who received axitinib as second-line therapy and 14 (48%) of 29 treated with

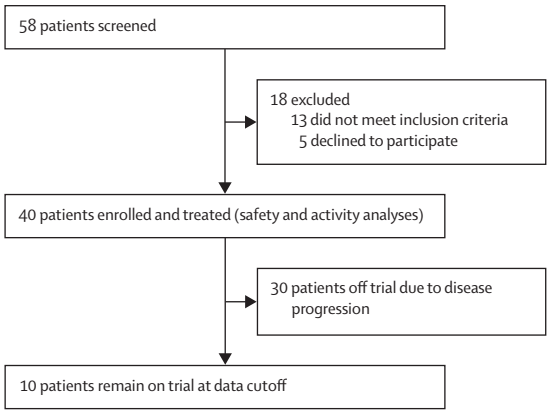

Figure 2: **Trial profile**

	Participants, N=40
Sex	
Male	29 (73%)
Female	11 (28%)
Age, years	64 (57–69)
Karnofsky Performance Status	
70	4 (10%)
80	7 (18%)
90–100	29 (73%)
International Metastatic Renal Cell Carcinoma Database Consortium Criteria	
Favourable	4 (10%)
Intermediate	30 (75%)
Poor	6 (15%)
Previous nephrectomy	
Yes	37 (93%)
No	3 (8%)
Sites of metastatic disease	
Lung	24 (60%)
Abdomen or retroperitoneum	21 (53%)
Lymph nodes	14 (35%)
Bone	9 (23%)
Liver	6 (15%)
Number of metastatic sites	
1	10 (25%)
2	16 (40%)
≥3	14 (35%)
Sarcomatoid component	
Yes	6 (15%)
No	34 (85%)

Values are n (%) or median (IQR).

Table 1: **Baseline characteristics**

	Participants, n=40
Number of previous therapies*	
1	11 (28%)
2	19 (48%)
3	9 (23%)
4	1 (3%)
Most recent therapy	
Nivolumab	25 (63%)
Ipilimumab plus nivolumab	6 (15%)
Nivolumab plus hypoxia-inducible factor inhibitor	3 (8%)
Atezolizumab	2 (5%)
Bevacizumab plus atezolizumab	2 (5%)
Durvalumab plus tremelimumab	1 (3%)
Durvalumab	1 (3%)
Best response to checkpoint inhibitor therapy†	
Partial response	8 (20%)
Stable disease	21 (53%)
Progressive disease	10 (25%)
Duration on previous checkpoint inhibitor	
<6 months	25 (63%)
≥6 months	15 (38%)
Median duration, months	4·8 (2·0–8·7)
Reason for checkpoint inhibitor discontinuation	
Disease progression	37 (93%)
Toxicity‡	3 (8%)
Time from checkpoint inhibitor discontinuation to axitinib initiation, months	1·1 (0·7–1·7)

Values are n (%) or median (IQR). *The majority of patients (28 [70%]) received previous VEGF-directed therapy. †Unknown for one patient. ‡One patient each: fatigue, pneumonitis, and colitis.

Table 2: **Previous therapies and response to immune checkpoint inhibitor**

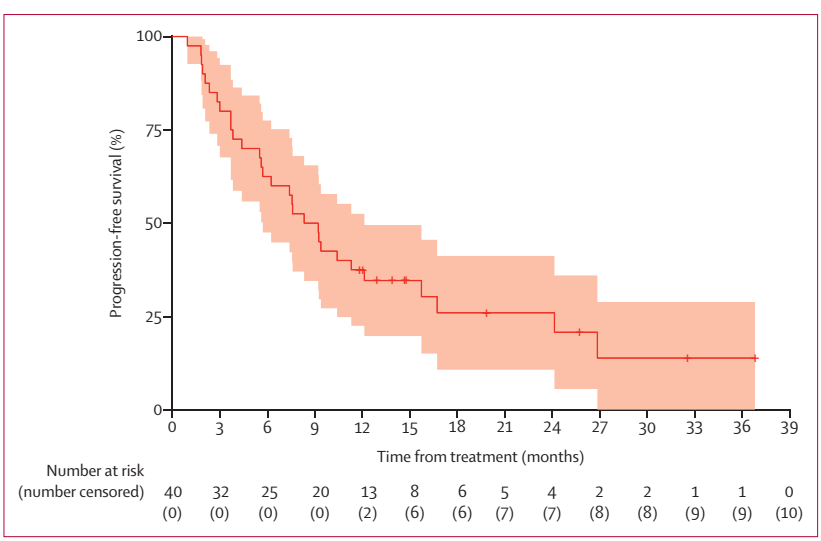

Figure 3: **Progression-free survival**

axitinib as third-line or later therapy achieved an objective response. Of the six patients who had a sarcomatoid component in their primary renal cell carcinoma, two (33%) achieved an objective response (two partial response, three stable disease, and one progressive disease). 15 (60%) of 25 patients who were on checkpoint inhibitor therapy for less than 6 months and three (20%) of the 15 who received therapy for more than 6 months achieved and objective response (p=0·057). In a post-hoc exploratory analysis, no clear association existed between previous checkpoint inhibitor therapy class and response to axitinib (PD-L1 *vs* PD-1 based regimens p=0·96; ipilimumab plus nivolumab *vs* nivolumab monotherapy p=0·67).

The median daily dose per patient was 5 mg twice daily, with a maximum dose of 9 mg twice daily and a minimum dose of 2 mg AM and 1 mg PM (required by one patient per provider discretion and approved by the principal investigator). 13 (33%) of 40 patients required dose reduction to less than 5 mg twice daily. Dose reductions were per protocol with the development of recurrent or persistent grade 2 or higher adverse events. The median number of dose changes for all patients was three (IQR 2–4). Overall, 85 (70%) of 121 of all dose changes occurred within the first 4 months of treatment.

A stable dose (defined as ≥3 months without dose change) was achieved in 29 (73%) of 40 patients with a median time to stable dose of 1·0 month (IQR 1·0–2·5). The median stable dose for all patients was 6·0 mg twice daily (4·7–7·0). The median stable dose for patients with complete or partial responses was 6·0 mg twice daily (4·7–7·0) and 5·0 mg twice daily (4·7–6·0) for patients with stable disease. For long-term responders (ie, those with RECIST complete or partial responses for ≥12 months), the median time to stable dose was 2 months (1·0–2·5) with a median stable dose of 7·0 mg twice daily (5·5–7·5). All patients with primary progressive disease withdrew before achieving a stable dose. Of the 16 patients with a complete or partial response who achieved a stable dose, nine (56%) had stable doses of 4 mg, 6 mg, or 8 mg twice daily, which are not included in the FDA-approved label.[19] In a post-hoc exploratory analysis, no clear relationship existed between dose and response (appendix p 1).

Data regarding breaks from therapy were available for 39 patients (one patient did not record breaks). Almost all patients (37 [95%] of 39) required at least one break while on treatment. The median number of breaks per patient was five (IQR 3–10). The median number of breaks per cycle was 0·81 (0·4–1·3), which translates into one break every 4·8 weeks.

The most common adverse events of any grade were fatigue (33 [83%] of 40), hypertension (30 [75%] of 40), and hand-foot syndrome (26 [65%] of 40; table 3). The most common grade 3 adverse events were fatigue (3 [8%] of 40), hypertension (24 [60%] of 40), and hand-foot syndrome (3 [8%] of 40; table 3). The only grade 4 adverse event was elevated lipase in one (3%) of 40 patients. Serious adverse events that were at least likely related to therapy occurred in eight (20%) patients.

The most common serious adverse events were dehydration (n=4) and diarrhoea (n=2). No patients discontinued therapy owing to adverse events. No deaths occurred.

Discussion

In this multicentre, phase 2 trial, individualised axitinib dosing in patients with metastatic renal cell carcinoma previously treated with checkpoint inhibitors did not meet the prespecified threshold for median progression-free survival, at 8·8 months (95% CI 5·7–16·6), but 18 (45%) of 40 patients achieved an objective response. Following the approval of nivolumab monotherapy for previously treated metastatic renal cell carcinoma,[1] ipilimumab plus nivolumab for treatment-naive intermediate and poor-risk metastatic renal cell carcinoma,[2] and axitinib plus pembrolizumab and axitinib plus avelumab for treatment-naive metastatic renal cell carcinoma,[20,21] data regarding therapy after checkpoint inhibitors is crucial. To our knowledge, these data represent the first prospective data for potential treatment options following checkpoint inhibitor-based therapy in metastatic renal cell carcinoma.

In addition to its highly selective targeting of VEGF-R 1, 2, and 3, clinical trial data support the use of axitinib following immunotherapy. The AXIS trial was a phase 3 randomised trial comparing axitinib with sorafenib as second-line therapy in patients with metastatic renal cell carcinoma who had previously received sunitinib, cytokines, bevacizumab plus interferon alfa, or temsirolimus. Of the 723 in the AXIS trial, 251 (35%) were treated with cytokines as their first-line therapy. The median progression-free survival for patients who received axitinib following front-line cytokine therapy was 12·2 months (95% CI 10·2–15·5) and overall survival was 29·4 months (95% CI 24·5 to not evaluable).[22] These data show clinical activity for axitinib following cytokine immunotherapy and, thus, support its consideration as an appropriate agent following checkpoint inhibitor therapy. However, the choice of an optimal tyrosine kinase inhibitor after checkpoint inhibitor therapy relies on the balance between scheduling, dosing, activity, and toxicity of individual tyrosine kinase inhibitors, because clear prospective data in this population do not exist.

A key challenge with tyrosine kinase inhibitor therapy is the substantial interindividual pharmacokinetic variability, which might contribute to the variable clinical response in patients.[23] However, some general principles of tyrosine kinase inhibitor pharmacokinetics have been well established. Early clinical trials with axitinib showed linear pharmacokinetics, such that higher doses of axitinib resulted in proportional increases in the plasma concentration.[24–27] In a pooled pharmacokinetic and pharmacodynamic analysis of axitinib from 17 clinical trials (590 patients),[16] a linear relationship between the dose of axitinib, plasma exposure, and area under the plasma concentration-time curve (AUC) was noted.

	Grade 1 and 2	Grade 3
Fatigue	30 (75%)	3 (8%)
Hypertension	6 (15%)	24 (60%)
Hand-foot syndrome	23 (58%)	3 (8%)
Decreased appetite	23 (58%)	1 (3%)
Diarrhoea	23 (58%)	2 (5%)
Dysphonia	22 (55%)	0
Nausea or vomiting	20 (50%)	0
Constipation	19 (48%)	0
Hypothyroidism	17 (43%)	0
Elevated creatinine	17 (43%)	0
Arthralgia or myalgia	13 (33%)	0
Anaemia	11 (28%)	1 (3%)
Thrombocytopenia	7 (18%)	0
Mucositis	4 (10%)	1 (3%)
Elevated haemoglobin	3 (8%)	1 (3%)
Weight loss	4 (10%)	0
Dehydration	0	4 (10%)
Elevated potassium	0	2 (5%)
Hypotension	0	2 (5%)
Lymphopenia	1 (3%)	1 (3%)
Headache	1 (3%)	1 (3%)
Infection (mandible)	0	1 (3%)
Elevated amylase	0	1 (3%)

Values are n (%). One patient (3%) had a grade 4 adverse event (elevated lipase). No deaths occurred.

Table 3: **Treatment-emergent adverse events**

Moreover, the probability of a response to treatment increased with each 100 h×ng/mL increase in AUC (p<0·0001). Both progression-free survival (13·8 months *vs* 7·4 months, p=0·003) and overall survival (37·4 months *vs* 15·8 months; p<0·001) were significantly longer in the high-AUC group (>300 h×ng/mL) versus the low-AUC group (<300 h×ng/mL).[16] These data indicate that higher exposure of axitinib is associated with improved clinical outcomes in patients with metastatic renal cell carcinoma. However, upward dose titration in individual patients is limited by toxicity, necessitating a balance between maximising exposure to a higher dose and achieving an acceptable level of toxicity. This trial did not show a relationship between drug dose and response, highlighting that different patients achieve different drug exposures with the same drug dose and that titration on the basis of toxicity best achieves the optimal axitinib exposure for clinical outcome in each patient.

On the basis of prospective clinical trial data showing improved outcomes with higher doses of axitinib, the regulatory approval of axitinib incorporated a dose-titration scheme to provide a framework for clinicians to maximise dose exposure.[17,19] However, in clinical practice, the FDA-approved dose-titration scheme is imprecise in its reliance on large incremental dose changes that can frequently result in overdosing and underdosing and compromise activity. In this study, a more nuanced toxicity-based

titration of twice daily dose escalations and reductions by 1 mg twice daily was implemented, on the basis of the hypothesis that this would maximise benefit and minimise risk. Specifically, toxicity-based titration was limited to considering only the axitinib-related toxicities of mucositis, diarrhoea, hand-foot syndrome, or fatigue, given their prevalence in previous clinical trials of axitinib and clinical experience that these toxicities most affect patients and drive drug discontinuation.[14] Additionally, breaks from therapy (3 days, per protocol) were allowed and generously applied to patients. This strategy permits recovery from lower grade cumulative toxicity and maintenance of a higher dose to maximise efficacy. Such a strategy should also be considered for an axitinib-based checkpoint inhibitor combination that is a standard of care initial therapy in metastatic renal cell carcinoma.[20] Although the relative importance of axitinib titration in checkpoint inhibitor combinations is unknown, optimising axitinib exposure with refined titration and breaks from therapy as in this study should be strongly considered.

Evidence for the activity of a toxicity-based dosing approach with VEGF-R tyrosine kinase inhibitors exists from multiple retrospective reports, including post-hoc analyses of large clinical trials.[28–31] Prospective data for toxicity-driven dose titration of sunitinib in treatment-naive metastatic renal cell carcinoma were also reported by Bjarnason and colleagues,[32] which showed a high proportion of patients achieving an objective response (46%, 95% CI 37–56), median progression-free survival (12·5 months, 9·6–16·5), and median overall survival (38·5 months, 28·3–not reached).

A particular challenge with dose titration of tyrosine kinase inhibitors is balancing increased activity with higher doses and the concern of increased toxicity.[33] It is precisely this delicate balance that necessitates trials that focus on smaller dosing changes to prevent incremental increases in toxicity. In this trial, the proportion of patients with grade 1–2 toxicities was relatively high, presumably as a result of the rapid titration scheme that dose-escalated patients every two weeks until grade 2 toxicity occurred. With the exception of hypertension, the few grade 3 adverse events and the fact that no patients discontinued for an adverse event reflect the more nuanced titration scheme and periodic treatment breaks. Moreover, the high proportion of patients with grade 3 hypertension (60%), which is higher than the aforementioned AXIS trial (16%), might actually serve as an indirect reflection of the success of this titration scheme as well as a marker of clinical activity.[20,34,35]

Although the titration scheme employed requires close monitoring from clinical staff to optimise patient-specific dose and adverse events, the majority (70%) of all dose changes occurred in the first 4 months of treatment. Thus, a dedicated dose-finding period in the initial months of therapy can result in optimal individualised dosing. Similarly, 56% of the objective responders had individualised stable doses of 4 mg, 6 mg, or 8 mg twice daily, which would probably not have been achieved using the package insert dosing that includes only doses of 2 mg, 3 mg, 5 mg, 7 mg, or 10 mg twice daily.[19]

This trial did not meet its primary endpoint, because it did not achieve a median progression-free survival of 9·5 months or more, and the 95% CI of 5·7–16·6 covered the hypothesised null value of 6·5 months. However, clinical activity (objective response achieved by 45%) and durability of response (67% of responses sustained for >12 months) was shown with axitinib on an individualised dosing scheme. Similarly, although the median progression-free survival was 12·2 months (95% CI 10·2–15·5) in a subgroup analysis of patients in the AXIS trial who had received previous cytokine therapy, these patients had not received previous VEGF tyrosine kinase inhibitor, whereas the majority of patients in this trial received at least two previous systemic therapies and most received VEGF-directed therapy.[22]

This study has several inherent limitations. Of note, it was a single-arm trial without a direct comparator cohort. Furthermore, the four clinical sites that participated in this trial are highly specialised academic centres with substantial experience managing patients with metastatic renal cell carcinoma, which might be reflected in the good progression-free survival, because the ability to manage toxicities could translate into longer duration on therapy. This study also consists of a relatively heterogeneous patient population with regard to the number of previous therapies and most recent checkpoint inhibitor treatment. Similarly, given the approvals of axitinib plus pembrolizumab and axitinib plus avelumab, it is difficult to ascertain whether the activity in this trial is a direct result of the more fine-tuned titration of axitinib or a synergistic consequence of adding axitinib to patients who recently received checkpoint inhibitor therapy. Despite these limitations, to our knowledge, these are the first prospective data highlighting the clinical activity of a specific VEGF-R tyrosine kinase inhibitor in patients with metastatic renal cell carcinoma following treatment with checkpoint inhibitor therapy. They also provide a framework and guidance for dose titration of axitinib that incorporates toxicity-based dosing, smaller dose titration increments, and treatment interruptions to maximise time on therapy and improve clinical outcomes.

In conclusion, although the prespecified threshold for clinically meaningful activity was not met, axitinib on an individualised titration scheme is feasible and showed activity in patients with metastatic renal cell carcinoma previously treated with checkpoint inhibitor therapy. Additional studies that continue to optimise individual dosing to extend duration of therapy and optimise clinical outcomes are warranted.

Contributors

MCO, LSW, BPH, TO, TDG, WKR, JAG, and BIR contributed to the design and concept of the trial. MCO, LSW, KDA, AMa, TO, AMo, TDG, WKR, JAG, BIR were involved in patient recruitment, patient management, or both. MCO, BIR, BPH, XSJ, and JMT were involved in data collection and analysis, and all authors contributed to data

interpretation. MCO and BIR drafted and revised the manuscript for content, with input from all authors. All authors reviewed and gave final approval of the manuscript submitted for publication.

Declaration of interests

MCO reports consulting and educational fees and grant support from Pfizer, during the conduct of this study, and consulting fees and speakers' bureau honoraria from Bristol-Myers Squibb and Exelixis, outside the submitted work. SKP reports consulting fees from Pfizer, Novartis, Aveo Oncology, Myriad Genetics, Genentech, Exelixis, Bristol-Myers Squibb, and Astellas, research and grant support from Medivation, and honoraria from Novartis, Medivation, and Astellas, outside the submitted work. LSW reports speakers' bureau honoraria from Pfizer, outside the submitted work. BPH reports consulting fees from Ignyta Inc, outside the submitted work. KDA reports speakers' bureau and consulting fees from Pfizer, Exelixis, and Bayer, outside the submitted work. NBD reports research funding from AstraZeneca, Hoffman-LaRoche, Pfizer, Merck, Incyte, Mirati Therapeutics, Seattle Genetics-Astellas, Calithera Biosciences, Taris BioMedical, Immunomedics, and Bristol-Myers Squibb and personal fees from Taris BioMedical, Calithera Biosciences, and Bristol-Myers Squibb, outside the submitted work. A Mo reports research funds to his institution from Genentech-Roche, Motive Medical Intelligence, Acerta Pharma, Merck, Novartis, Seattle Genetics, Mirati Therapeutics, and Bristol-Myers Squibb, advisory board fees from Genentech-Roche, and honoraria for literature review from Motive Medical Intelligence, outside the submitted work. WKR reports research and grant funding from Pfizer, Novartis, TRACON Pharmaceuticals, Bristol-Myers Squibb, Incyte, Calithera, Peloton, Roche, Tempus, and AstraZeneca and consulting or advisory fees or honoraria from Merck, Johnson & Johnson, Calithera, Pfizer, Roche, and ImmuNext, outside the submitted work. They also own the patent for the ClearCode34 risk prediction biomarker for renal cell carcinoma (patent number US 2013/0005597 A1). JAG reports consulting fees from Bayer, Clovis, Eisai, Merck, and Astellas and teaching and education fees from Sanofi, Bayer, and Merck, outside the submitted work. BIR reports grants and personal fees from Pfizer, during the conduct of the study, and grants and personal fees from Bristol-Myers Squibb, Merck, Roche, Peloton, Aveo Oncology, and Astra-Zeneca, outside the submitted work. JMT, XSJ, AMa, TO, and TDG declare no competing interests.

Data sharing

Qualified researchers can contact the corresponding author (MCO) to obtain specific de-identified clinical trial data. Individual data sharing agreements will need to be obtained through relevant Cleveland Clinic departments (eg, institutional review board or legal department).

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