Kidney Cancer 3 (2019) 213–225
DOI 10.3233/KCA-190077
IOS Press

Review

Individualization of Dose and Schedule Based On Toxicity for Oral VEGF Drugs in Kidney Cancer

Ambika Parmar and Georg A. Bjarnason*
Sunnybrook Odette Cancer Centre, Toronto, Ontario, Canada

Abstract. The introduction of oral vascular endothelial growth factor receptor tyrosine kinase inhibitors therapy has been associated with major improvements in outcome for patients with metastatic kidney cancer. Each drug has been licensed with rigid dosing criteria that are not optimal for all patients. This paper reviews the growing body of evidence suggesting that individualized dosing based on toxicity may be associated with optimal drug exposure for each patient and improved outcome both in the metastatic and adjuvant setting.

Keywords: Kidney neoplasm, medicine individualized, drug dosing biomarker, vascular endothelial growth factor receptor tyrosine kinase inhibitors therapy

INTRODUCTION

This review will discuss the available data suggesting that patients with metastatic renal cell cancer (mRCC) that experience a degree of toxicity associated with their oral vascular endothelial growth factor receptor tyrosine kinase inhibitors therapy (VEGFR-TKI) may do better than those with minimal toxicity. If toxicity can be used as a surrogate biomarker for optimal pharmacokinetics (PK) and pharmacodynamics (PD) for each patient, the many complex variables such as interindividual differences in VEGFR-TKI absorption, metabolism, interactions with other drugs and food [1] and genomic polymorphisms could be accounted for by toxicity driven dose and schedule changes. This strategy might then optimize drug exposure for each patient and improve outcomes. Sunitinib will be discussed first since most of the available data has been generated with this drug and a prospective trial of individualized sunitinib has been recently published [2]. Some of the general concepts that may also apply to other VEGFR-TKIs are discussed in this section. This will be followed by a summary of available data for axitinib, pazopanib, cabozantinib and sorafenib.

SUNITINIB

Sunitinib is a first line therapy for mRCC with a recommended starting dose and schedule of 50 mg daily for 28 days followed by a 14-day break (4/2 schedule) with dose reductions for toxicity to 37.5 mg (75% of starting dose) and 25 mg (50% of starting dose) on the same schedule.

The half- life of sunitinib and its active metabolite (SU12662) is 40–60 hours and 80–110 hours respectively. There is a large interindividual variation of 30–150 ng/ml in Sunitinib through concentration at a 50 mg per day dose [3] and several SNPs have been reported that can play a role in the interindividual variation of sunitinib PK [4–8].

Drug exposure is important for the activity of sunitinib and other VEGFR-TKIs. A meta-analysis of several studies that included 149 mRCC patients

*Correspondence to: Dr. Georg A. Bjarnason, Division of Medical Oncology, Sunnybrook Odette Cancer Centre, 2075 Bayview Ave, Toronto, ONT, Canada, M4N 3M5. Tel.: +1416 480 5847; Fax: +1416 480 6002; E-mail: georg.bjarnason@sunnybrook.ca.

ISSN 2468-4562/19/$35.00

treated with sunitinib found a longer time to progression (TTP) and overall survival (OS) as well as a higher objective response rate (ORR) in patients with a higher (sunitinib plus SU12662 > 800 ng x h/ml) steady state area under the curve (AUC) [9]. The improvement in OS associated with a higher AUC was confirmed in another study on 55 mRCC patients using a higher cut-off value for AUC (>1,973 ng x h/ml) [4]. However, in 146 patients receiving the standard 4/2 schedule of sunitinib [10] there was no correlation between sunitinib "steady state trough concentrations values" on day 29 (cycle 1) and the need to dose reduce based on toxicity. Therefore PK-guided dosing alone cannot be used to individualize sunitinib dosing [11]. This lack of correlation between PK and toxicity for sunitinib, has been confirmed for pazopanib and axitinib [11–13]. While a high AUC is important, it alone can't predict toxicity or optimal PD. Gotink et al found that intratumoral and skin concentrations of sunitinib in mice and intratumoral concentration in patients were 10.9 ± 0.5 and 9.5 ± 2.4 mmol/L, respectively, whereas plasma concentrations were 10-fold lower, 1.0 ± 0.1 and 0.3 ± 0.1 mmol/L, respectively [14]. Plasma concentrations therefore do not truly reflect the intratumoral concentration of sunitinib, due to its high volume of tissue distribution. The intratumoral concentration may therefore be better reflected by the concentration in normal tissue that is in turn reflected by normal tissue toxicity.

VEGFR-TKI PK parameters can decline over time in spite of constant dosing as has been described for both sorafenib [15, 16] and pazopanib [17, 18]. A similar decline in sunitinib PK was found in 17/22 patient in the study on individualized sunitinib [2]. This may explain why some patient experience some reduction in side effects as they stay on a constant dose of VEGFR-TKIs long-term and may be an argument for continuous dose/schedule changes to optimize drug exposure.

One mechanism of sunitinib resistance in 786-O renal and HT-29 colon cancer cells was found to be mediated by lysosomal sequestration of the drug [14]. This resistance mechanism was reversible with recovery in drug-free culture. A similar reversible resistance to sorafenib has been found in human mRCC xenograft models with intermittent sorafenib therapy being more active than continuous exposure [19, 20]. These data suggest that intermittent rather than continuous delivery of VEGFR-TKIs may be more active than continuous therapy. This concept is supported by the EFFECT trial comparing sunitinib 50 mg on the 4/2 schedule to a continuous delivery at 37.5 mg [10]. The 4/2 schedule was associated with a numerically longer PFS and statistically superior time to deterioration, a composite end point of death, progression, and disease-related symptoms ($P = 0.034$). The continuous dosing schedule for sunitinib has been abandoned in mRCC but remains the recommended schedule for other VEGFR-TKIs used for RCC without any scientific rationale.

Steady state blood levels for sunitinib are reached after 10–14 days [21]. This time to maximum AUC is consistent with micro-bubble ultrasound data [22] for patients responding to sunitinib which demonstrated that most of the benefit from sunitinib may be achieved by day 14. In 8 patients, studied at baseline and after 7 days and 14 days on therapy, tumor blood volume (a measure of antiangiogenic activity) decreased on day-7 and again on day-14. However, in 6 patients studied at baseline, and after 14 days and 28 days on therapy, blood volume decreased on day-14 compared to baseline but remained stable or increased on day-28 versus day-14 in 4 patients. Most patients showed a rebound in blood volume after a 14-day treatment break. Taken together the above data on PK and PD suggest that a shorter duration of therapy with breaks may be better than a premature dose reduction, and that the treatment break should be as short as possible to avoid tumor progression that can occur during treatment interruption [22–25].

Several retrospective series have shown that patients that do not need dose/schedule changes from the standard 50 mg 4/2 sunitinib schedule to manage toxicity have a worse outcome. This is consistent with early report showing a better outcome in mRCC patients that developed hypertension, hypothyroidism or hand foot syndrome while on VEGFR-TKI therapy [26, 27].

This was first documented in a retrospective analysis of 172 patients with an inferior outcomes in patients experiencing minimal toxicity on the standard 50 mg 4/2 schedule compared to patients that developed toxicity and required dose/schedule modifications [22]. Dose/schedule modifications (DSM) were done to keep toxicity (hematological, fatigue, skin, and gastrointestinal) at $\leq$ grade-2. Patients that needed schedule modifications at the 50 mg dose or dose reductions and schedule modifications because of toxicity had a PFS (10.9–11.9 months respectively) and OS (23.4–24.5 months respectively) that was significantly better than the PFS (5.3 mo; $P < 0.001$) and OS (14.4 mo; $P < 0.03$ and 0.003 respectively) for the standard schedule (50 mg, 28/14). Several

Table 1
Retrospective analysis of the impact of dosing changes for toxicity on outcome in three prospective trials

Study	Phase-III sun vs. Inf		Effect		Comparz			
Drug	Sunitinib 4/2		Sunitinib 4/2		Sunitinib 4/2		Pazopanib	
Dosing	No dose reduction	Any dose reduction	No dose reduction	Any dose reduction	No dose reduction	Any dose reduction	No dose reduction	Any dose reduction
N	181	194	95	51	270	277	308	246
PFS Mo	8.1	**14.0**	5.8	**13.4**	5.5	**13.8**	7.3	**12.5**
95% CI	(6.3–10.6)	(13–16.2)	(3.9–8.5)	(9.8–19.8)	(4.3–8.1)	(11.1–16.4)	(5.3–8.3)	(10.9–15.0)
OS Mo	–	–	–	–	18.1	**38.0**	21.7	**36.8**
95% CI					(14.1–23.4)	(31.5–NE)	(18.1–24.7)	(33.1–NE)
ORR%	25.4	**60**	22.12	**51**	16	**34**	22	**42**
95% CI					(11.9–20.7)	(28.0–39.1)	(17.1–26.4)	(36.1–48.4)
P	–	–	–	–	$P < 0.001$ for PFS, OS and ORR		$P < 0.001$ for PFS, OS and ORR	

other retrospective series have subsequently confirmed this observation of an inferior outcome in patient that do not need sunitinib dose/schedule adjustments for toxicity [28–32].

Retrospective analysis of three prospective randomized trials [10, 33, 34] are of particular interest (summarized in Table 1). A retrospective analysis [11] of the phase-III trial comparing sunitinib to Interferon (375 patients) [33] and the 4/2 arm of the Phase-II EFFECT trial (146 patients) [10] showed an inferior ORR and median PFS in patients that continued on the standard schedule with minimum toxicity vs. those that required dose changes due to toxicity. The impact on OS was not reported. A similar significant impact on PFS, OS and ORR based on the need for dose reduction and treatments breaks $\geq$7 days due to toxicity was reported for both sunitinib and pazopanib in a *post hoc* analysis of the COMPARZ trial [34, 35] (Table 1).

These retrospective data show that toxicity may be used as a surrogate for adequate drug exposure and to guide individualized dosing. Furthermore, these data raise the question whether patients with minimal toxicity on the maximum approved dose of an oral VEGFR-TKI should be dose escalated. In mice, sunitinib-induced resistance can be overcome, in part, by increasing the dose, and a potential role of epigenetic changes associated with sunitinib resistance was suggested [36]. This study also reported a PFS benefit in 17 patients that were dose escalated to 62.5 mg or 75 mg after early progression. A retrospective analysis of 25 patients, progressing on sunitinib 50 mg, reported a benefit from dose escalation to 62.5 and 75 mg [37]. At standard doses, 60% and 16% of patients had a PR and SD as best response respectively for a median duration of 11.4 months (95% CI: 3.0–20.7). A total of 6 patients (24%) had progressing disease (PD) as best response. After progression, 36% and 28% had PR and SD on higher doses of sunitinib respectively for a median duration of 7.8 months (95% CI: 6.3–12.4). The median PFS1, PFS2 and OS were 6.1 months (95% CI: 2.3–19.4), 6.7 months (95% CI: 3.1–8.4) and 63.7 months (95% CI: 26-NR) respectively. Three patients that had a PD on a 50 mg dose had a clinical benefit (1 PR, 2 SD) at the higher doses. Another way to increase the drug exposure for sunitinib is to give the drug without breaks [38, 39]. At progression, 34 patients with mRCC who had mild toxicity were given sunitinib 50 mg once daily continuously and continued until disease progression or toxicity. With continuously dosed sunitinib, 2 (5.9%) patients achieved PR, 27 (79.4%) had SD, and the disease still progressed in 5 (14.7%) patients. Tumor size was reduced in 10 (38.2%) patients [39].

INDIVIDUALIZED SUNITINIB STUDY:

A prospective phase-II study of individualized sunitinib dose and schedule was recently published [2]. Based on the data presented above, it was hypothesized that toxicity-driven dose and schedule changes would optimize drug exposure and improve outcome for each patient. The eligibility criteria for the study were similar to the EFFECT trial [10] for which median PFS (8.5 months) on the 4/2 arm was used as the historical control to power the study. One hundred and seventeen patients with metastatic clear cell renal-cell cancer started sunitinib 50 mg/day with the aim to treat for 28 days. Treatment breaks were reduced to 7 days from the usual 14 days. Sunitinib dose and number of days on therapy were individualized based on toxicity aiming for $\leq$ grade-2 toxicity (oral mucositis, diarrhea, hand-foot syndrome, neutropenia, thrombocytopenia, and fatigue) with dose escalation in patients with minimal toxicity. If grade-2 toxicity developed before day 28, sunitinib

Table 2
Dose and schedule distribution for 108 patients on optimized dosing

Sunitinib Dose (mg)	Schedule (days on/off)	Patients currently on or came off therapy on this dose and schedule	
75	18/7	1	
75	14/7	4	20 patients (18.5%)
75	10/7	1	dose escalated
75	7/7	2	
62.5	16/7	2	Median dose intensity (DI)
62.5	14/7	4	1.5 at 75 mg
62.5	12/7	1	1.3 at 62.5 mg
62.5	10/7	1	
62.5	7/7	4	
50	28/7	6	7 patients (6.5%) on for 28 days,
50	28/14	1	DI = 1
50	25/7	1	
50	24/7	2	In 50 patients (46.3%)
50	16/7	2	50 mg dose maintained with fewer
50	14/7	22	days on Rx.
50	13/7	1	Would have been dose reduced by
50	12/7	1	standard criteria
50	9/7	2	DI = 0.9
50	7/7	19	
37.5	Continuous	4	
37.5	21/7	1	21 patients (19.4%) dose reduced
37.5	14/7	5	to 37.5 mg,
37.5	11/7	2	
37.5	9/7	1	DI = 0.8
37.5	7/7	8	
25	Continuous	2	10 patients (9.3%) reduced to 25 mg,
25	14/7	4	
25	7/7	4	DI = 0.5

was held for 7 days. Therapy was then continued on a 50 mg dose with the number of days on therapy individualized based on toxicity. The dose was only reduced to 37.5 mg and then 25 mg if patients did not tolerate a 50 mg or 37.5 mg dose respectively for at least 7 days. Patients with $\leq$ grade-1 toxicity after 28 days on therapy were dose escalated to 62.5 mg and then 75 mg on a schedule of 14 days on and 7days off and the number of days on therapy then individualized up or down based on toxicity.

All 117 patients started therapy but nine came off study due to progression and toxicity before confirmatory imaging was done. Of 108 patients, where optimal dosing was established, 7 were still on therapy. Table 2 shows the dose and schedule when therapy was discontinued for the 108 patients where optimal dosing was established. There was a large interindividual variability in the optimal dose and schedule. The median time to optimal dosing was 4 months (range 1.8–13.2) with some patients adding days on therapy or dose escalating during therapy when toxicity resolved to some extent. Dose intensity at the optimal dose and schedule was calculated as previously described [31]. In 20 patients (18.5%) dose was escalated to 62.5 mg (12) and 75 mg (8), with a dose intensity of 1.3 and 1.5 respectively. In 50 patients (46.3%), a 50 mg dose was continued but for less than 28 days (dose intensity 0.9), thus avoiding a reduction to 37.5 mg as per standard dosing criteria. In 21 patients (19.4%) dose was reduced to 37.5 mg (dose intensity 0.8), and in 10 patients (9.3%) dose was reduced to 25 mg (dose intensity 0.5). Six patients received continuous dosing at 25 mg (2) and 37.5 mg (4) rather than dose escalate to the next higher dose level as per protocol due to patient/physician decision.

Most patients settled on a dose and schedule that resulted in noticeable toxicity, between grade-1 and grade-2, that they could accept long term. Dose reductions were required for toxicity in 31/117 patients (26.5%) and therapy was discontinued due to toxicity in 9/117 (7.7%). In previous sunitinib trials, 50% of patients required dose reduction [33] and 18–20% discontinued due to toxicity [33, 34]. There were no significant changes during therapy in the mean quality of life scores for the FACT-G and the FKSI-DRS ($p = 0.58$ and 0.10 respectively).

The null hypothesis for the primary endpoint was a progression free survival (PFS) of 8.5 months based on the 4/2 arm of the EFFECT trial that had similar eligibility criteria. The null hypothesis was rejected ($p < 0.001$) with a median PFS of 12.5 months (95% CI: 9.6–16.5). The median OS was 38.5 months (95% CI: 28.3-not reached). The ORR (46.1%), and SD rate (38.5%) translated into a clinical benefit for 84.6% of patients. There was no association between ORR, PFS or OS vs. dose given, duration of therapy or dose intensity. One dose, dose intensity or duration of therapy does not fit all. While no direct comparison can be made between trials, the efficacy data compare favorably to contemporary data for sunitinib, axitinib and pazopanib [10, 34, 40] and to recent data for IMDC intermediate and poor risk patients [41, 42].

In 46 patients with PK data at baseline and after optimal dosing was established the sunitinib and SU012662 concentration increased (standard error) by 20.5 (5.9) and 12.7 (2.8) ng/ml respectively in those that were dose escalated and decreased by 16.2 (15.6) and 12.1 (5.1) ng/ml respectively in those that were dose reduced. After dose individualization, the mean concentration was not different between dose levels for sunitinib ($p = 0.10$) but still different for SU012662 ($p = 0.01$) showing that this dosing method leads to less interindividual differences in PK but some differences remain emphasizing the importance of pharmacodynamics for toxicity and outcome.

In another study, 45 patients given toxicity-adjusted dosing of sunitinib (85% on sunitinib on the 2/1 schedule) had drug level monitoring every 6 weeks. The main endpoint of study was intra-patient drug level variability, that remained unacceptably high in 25% of patients in spite of toxicity adjusted dosing [43]. At the end of the day, intratumoral drug exposure, that are better reflected by toxicity, may be more important for optimal outcome for each patient than the drug levels in blood.

Dose individualization is commonly used in Canada based on the experience of investigators that entered patients on the above sunitinib individualization trial. In an analysis using the prospective Canadian Kidney Cancer Information System [44], the median OS (37.9 vs. 22.3 months) and time to treatment failure (12.9 vs. 5.6 months) were both improved ($p < 0.001$) for individualized sunitinib ($n = 355$) compared to standard schedule sunitinib ($n = 151$) respectively. These real-life data for unselected kidney cancer patients treated first line support the data on individualized sunitinib.

AXITINIB:

Axitinib is a potent and selective inhibitor of VEGF-R 1, 2 and 3. It has a short half-life of 2.5 – 6 hours, noticeably shorter than that for sunitinib. Axitinib was approved in previously treated mRCC patients based on a superior PFS compared to sorafenib [45]. A first line trial vs. sorafenib did not meet its primary endpoint but showed good activity with an ORR of 32% and PFS of 10.1 Months [40]. Recently axitinib in combination with Pembrolizumab has been approved in the first line setting having shown significantly better ORR, PFS and OS vs. sunitinib [46].

A population PK analysis for axitinib, including data from 17 trials (383 healthy volunteers, 181 mRCC patients, 26 other solid tumor patients), showed a linear relationship between dose, plasma exposure and AUC. There was a significant interindividual variability in AUC at 4 weeks. High AUC and increase in diastolic blood pressure were both independent predictors of better response and longer PFS and OS [12]. The probability of achieving PR increased with every 100 ng x h/ml increase in AUC and both PFS (13.8 months vs. 7.4 months, $p = 0.003$) and OS (37.4 months vs 15.8 months; $p < 0.001$) were significantly longer in the high-AUC group (>300 h×ng/mL) vs. the low-AUC group (<300 h×ng/mL) respectively. This association between a higher AUC and better outcome has been confirmed in one study using dynamic contrast enhanced MRI as a surrogate for vascular response and in another study of patients with UGT1A1 polymorphism [47, 48].

In a phase-II dose titration study, patients having received axitinib 5 mg BID for 4 weeks, with BP ≤ 150/90, on ≤ 2 drugs for hypertension and no grade-3 or grade-4 axitinib related toxicity, were randomized to axitinib dose titration (to 7 mg BID and then 10 mg BID) vs. placebo titration [49]. Of 213 patients enrolled, 112 were randomized but 91 remained on 5 mg BID dose or lower based on toxicity. Response rate was significantly improved in the active vs. placebo titration arm (54% vs. 34%, $p = 0.019$), but there was no significant difference in PFS even though PFS was high in both titrations arms (14.5 vs. 15.7 Mo). In the non-randomized arm, where patient could not be dose escalated due to toxicity, the response rate was 59% and PFS 16.6 Mo. There was no difference in OS [50]. The fact that patients with hypertension and/or on antihypertensive therapy were excluded from dose escalation may have underestimated its value. This group of patients

is destined to do well on axitinib therapy [51]. Several patients who escalated to 7 mg BID and higher had to quickly reduce to 5 mg BID dosing or lower, suggesting that this dose titration schema for Axitinib was too steep for some patients. Although the hazard ratio for PFS favored the titration arm (HR = 0.85), this was not statistically significant.

A phase-II study was conducted to study a more refined individualized dosing for Axitinib based on toxicity [52]. Patients started axitinib 5 mg BID. In the absence of grade 2 mucositis, diarrhea, hand-foot syndrome, or fatigue, dose titration was done every 14 days in 1 mg increments up to 10 mg BID. Other toxicities, notably treatable hypertension, were not considered for titration decisions. If grade 2 toxicity occurred, therapy was held for 3 days, and then resumed at the same dose. Recurrent grade 2 toxicity despite treatment breaks or grade 3–4 toxicity resulted in dose reduction in increments of 1 mg BID. This individualized dosing continued until a steady dose, was identified. All 40 patients entered on study had immunotherapy as the last therapy before axitinib and most had received at least 2 therapies including previous VEGF directed therapy (70%).

The study hypothesis was that individualized axitinib therapy would improve the PFS from the 6.5 months, previously reported in retrospective reviews for VEGF targeted therapy post immunotherapy [53, 54], to 9.5 months. The trial did not meet this primary endpoint but showed good clinical activity in this cohort of heavily pretreated patients with a PFS was 8.8 months (95% CI 5.7–16.6), and a 45% ORR (1(3%) CR, 17 (43%) PR). Eighteen patients (45%) had SD and 4 (10%) had PD. Of the 18 patients who responded to axitinib, 12 (67%) had a sustained response of more than 12 months. OS was not reported. 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 and 13 (33%) patients required dose reduction to less than 5 mg twice daily. The median number of dose changes for all patients was three (interquartile range 2–4) with 70% of all dose changes being done within the first 4 months. A stable dose (defined as $\geq$3 months without dose change) was achieved in 73% of patients with a median time to stable dose of 1.0 month (interquartile range 1.0–2.5). The median stable dose for all patients was 6.0 mg BID (4.7–7.0). Of the 16 patients with a CR or PR who achieved a stable dose, nine (56%) had stable doses of 4 mg, 6 mg, or 8 mg BID, which are not included in the FDA-approved label. In a *post-hoc* exploratory analysis, there was no clear relationship between dose and response. This agrees with the data from the sunitinib individualization study described above where there was no association between ORR, PFS or OS vs. dose given or vs. dose intensity [2]. 95% of patients required at least one break while on treatment. The median number of breaks per cycle was 0.81 (0.4–1.3). This was expected and built into the protocol in an effort to maximize drug exposure as opposed to aiming for a dose that could be given continuously without a break. The 3-day break on this study versus the 7-day break in the sunitinib study is possible because of the much shorter half-life of axitinib vs. sunitinib.

Since patients were treated to toxicity the incidence of grade-1 and -2 toxicities was relatively high, but grade-3 toxicity, other than hypertension, was rare and with no patients discontinuing therapy due to toxicity. The proportion of patients with grade-3 hypertension (60%) on this study is much higher than on the AXIS [55] trial (16%) and might be an indicator of a successful titration schedule [51]. The authors suggested this scheduling could be used when axitinib is given in combination with immunotherapy.

The above data, indicating that a higher exposure to axitinib is associated with better clinical outcomes in the metastatic setting have now been extended to the adjuvant setting. The ATLAS trial compared axitinib vs. placebo in patients with locoregional RCC at risk of recurrence after nephrectomy [56]. Patients ($n = 228$) requiring dose reduction for toxicity had a longer disease free survival (DFS) than those ($n = 109$) with a stable dose (HR = 0.458, CI: 0.305–0.687, $P = 0.0001$). However, patients able to tolerate a dose increase ($n = 19$) did not have a different DFS vs. stable dose patients (HR = 1.936, CI: 0.937–3.997, $P = 0.0685$). This suggests a relationship between axitinib exposure and DFS in the adjuvant setting as has been reported with pazopanib in the adjuvant PROTECT study [13].

PAZOPANIB

Pazopanib was approved in the 1st line setting for mRCC based on a randomized study showing improved PFS versus. placebo [57]. A subsequent phase 3 study showed similar PFS, OS and ORR vs. sunitinib 1st line but differences in toxicity profiles [34].

Pazopanib, an inhibitor of VEGFR1, 2 and 3, PDGFR, c-Kit and FGFR1, 3 and 4, is metabolized mainly by CYP3A4, to form its metabolites (M1-M7)

[58]. Only the M2 metabolite has a bioactivity similar to pazopanib. Pazopanib has a half-life of 31.1 hours, but there is a significant intrapatient (25–27%) [17, 59] and interpatient variability in PK (67–72%) [60, 61]. Administration of pazopanib with food increased Cmax and AUC by approximately two-fold and the use of medications that alter gastric pH also contribute to the inter- and intra-patient variability of pazopanib pharmacokinetics.

An analysis of the relationship between plasma pazopanib concentrations, clinical efficacy and safety in patients with mRCC [62] was based on data from 225 patients with locally advanced or metastatic RCC treated with pazopanib (800 mg/day) in a single-arm phase II trial [63]. With the approved dose of 800 mg once daily, approximately 20% of patients did not reach the pharmacokinetic threshold of Cmin C20 mg/L. Median PFS (52 weeks vs. 19.6 weeks) and ORR (37.9% vs. 6.9%) were significantly better in patients with week-four Ctrough levels above 20.5μg/ml. Likewise, the % of pazopanib refractory patients was more than double when the week-four level was less or equal to 20.5μg/ml (38%) compared with patients with a week-four Ctrough above 20.5μg/ml (11%).

The rationale for individualized pazopanib therapy based on PK data has been reviewed [18] and this concept has been tested in two small trials. The first study was a prospective trial in 30 patients with advanced solid tumors [61]. This study set Cmin of 20.0 mg/L as the target exposure. At weeks 3, 5, and 7, the pazopanib dose was increased if Cmin was <20.0 mg/L and toxicity was below grade 3. This dosing algorithm led to patients being treated at doses ranging from 400 to 1800 mg/day. In 57% of patients ($n = 17$) the ideal C-trough level (20.5μg/ml) was not achieved by taking a fixed dose of 800 mg QD but with dose escalation above 800 mg the Cmin in 10 of these patients rose significantly from 13.2 to 22.9 mg/L. The overall variability in Cmin was reduced from 71.9% on the fixed-dose schedule (week 2) to 33.9% (week 8) after applying the pharmacokinetically-guided dosing algorithm. This study showed that pazopanib can be safely dose escalated in patients with minimum toxicity and that a dose of 800 mg/day is inadequate for many patients. It also showed that PK guided dosing is not useful in 60% of patients. In a subset of patient treated continuously at the 800 mg dose the AUC decline over time.

In another study [17], 13 patients were treated with pazopanib for 3 consecutive periods of 2 weeks. During the first period, all patients received 800 mg pazopanib once daily to reach steady-state exposure. During the second period, patients either received a PK-guided individualized pazopanib dose or the registered fixed 800 mg dose. During the third period, these two dosing regimens were switched. PK-guided dosing did not reduce the inter-patient variability in pazopanib exposure, and the authors concluded that PK guided dosing was not useful for this drug. Overall, 53.9% of patients in the AUC-guided dosing arm and 46.2% of patients in the fixed-dosing arm achieved the target exposure. Pazopanib AUC0-24hr decreased 17% over time in spite of constant dosing as has been shown for Sorafenib [15, 16].

In previous clinical trials for mRCC, pazopanib has been given on a continuous schedule with dose reduction from the standard 800 mg dose for patients that develop toxicity on continuous therapy. Dose escalation in patients with no toxicity has not been recommended. The data discussed above highlight the significant inter and intra patient variability in PK, the importance of adequate drug exposure for outcome and that PK guided dosing is not a clinically useful method to deal with this. Using toxicity as a surrogate for adequate pazopanib dosing, as has been studied with sunitinib and axitinib, with treatment breaks rather than continuous dosing, has not been formally studied. Toxicity driven individualized pazopanib dosing with treatment breaks is further supported by the a *post hoc* analysis of the COMPARZ trial [34, 35] described above and in Table 1. Patients that needed dose reduction and treatments breaks due to toxicity, a surrogate for adequate dosing, had a significantly better PFS, OS and ORR than those that remained on the standard 800 mg dose without significant toxicity. This was true for both pazopanib and sunitinib patient in this *post hoc* analysis.

These data regarding the importance of optimal pazopanib drug exposure in the metastatic setting have now been extended to the adjuvant setting. The PROTECT study evaluated pazopanib as adjuvant therapy after nephrectomy [64]. The starting dose in this trial was reduced from 800 mg to 600 mg due to perceived high discontinuation rates. The study failed to show any DFS benefit in the patients starting at a 600 mg dose (primary endpoints, 571 patients), but the patients starting at 800 mg had a 31% reduced risk of recurrence or death (secondary endpoint, 198 patients). These results led to a study to evaluate if pazopanib drug exposure (Cthrough) correlated with efficacy and safety in the adjuvant

setting based on PK sampling from 311 patients at week 3 and 5 and 250 patients at week 16 and 20 [13]. More than 90% of these patients started on the 600 mg dose and only 21% of all patients started on this dose level had a dose escalation to 800 mg. Patients with higher early Ctrough quartiles achieved longer DFS (adjusted HR, 0.58; 95% confidence interval, 0.42–0.82; $P = 0.002$). Patients achieving early or late Ctrough >20.5 mug/mL had significantly longer DFS: not estimable (NE) versus 29.5 months, $P = 0.006$, and NE versus 29.9 months, $P = 0.008$, respectively. Dose intensity up to week 8 did not correlate with DFS. This is consistent with previous data that show that drug exposure as opposed to given dose determines clinical effect. The proportion of AE-related treatment discontinuation and grade 3/4 AEs, with the exception of hypertension, was not correlated to Ctrough. These data and the data for adjuvant Axitinib [56] suggest that toxicity driven dose and schedule changes may be important not only in the metastatic setting but also in the adjuvant setting [65].

CABOZANTINIB

Cabozantinib is approved for the treatment of renal cell carcinoma following anti-angiogenic therapy based on the METEOR study [66, 67]. The recommended starting dose is 60mg per day given continuously. Cabozantinib has a long terminal plasma half-life (~120 h) and accumulates fivefold by day 15 following daily dosing based on AUC. This is similar to the data for sunitinib that show that the max AUC was obtained after 10–14 days. Continuous cabozantinib dosing for more than 15 days may not be required for all patients to optimize drug exposure.

Cabozantinib exhibited a high interpatient PK variability in mRCC patients on the METEOR study (coefficient of variation for clearance values CL/F (46%)) [68]. The inter-subject variability (%CV) in healthy volunteers following a single capsule or tablet dose ranged from 20 to 59% for AUC values and from 28 to 72% for Cmax across the studies. The within-subject variability was estimated to be 39% for Cmax and 28% for AUC values in the capsule-tablet bioequivalence study. The inter-subject variability in cancer patients was 42–43% for Cmax and 34% for AUC after a single dose, and 37–43% for Cmax and 38–43% for AUC at steady state. Exposure variability for cabozantinib in cancer patients and healthy volunteers appears similar [69]. These data highlight, as has been shown for other VEGFR-TKI's, the significant interindividual variability in the PK of cabozantinib and the fact that one dose or schedule will not fit all.

Based on exposure response (ER) model analysis for the METEOR study, higher cabozantinib exposures resulting from lower cabozantinib clearance was predicted to increase the dose modification rate of cabozantinib due to toxicity. While the ER model analysis demonstrated that reducing cabozantinib exposure with dose reduction was expected to decrease the risk of fatigue/asthenia, HFS, hypertension, and diarrhea while maintaining a clinical benefit [68]. Among the 282 patients evaluated in the METEOR study, exposure response analysis (ER) evaluated the effect of Cabo exposure at steady state on PFS and toxicity at various coefficient of variation for clearance values (CL/F). CL/F values ranged from 0.51 to 7.24 L/hr. Because of variations in CL/F values, exposure may be similar at different doses. Thus, the exposure at 40 mg dose for a low CL/F (1.3 L/hr) is predicted to be similar to a 60 mg dose for a typical CL/F (2.23 L/Hr). And the exposure of Cabo at 40 mg for a typical CL/F appeared to be comparable to a 60 mg dose for a high CL/F (3.3 l/hr). Patients with a high CL/F may have less favorable PFS at a starting dose of 40 mg vs. the 60 mg dose. Patients with a low CL/F are predicted to have less toxicity at the 40 mg dose vs. the 60 mg dose [70]. Dose reductions due to adverse events were required in 64% of the cabozantinib treated patients (331 patients in safety population) in the METEOR study [71]. The median average dose was 42.8 mg. Treatment discontinuation due to adverse events occurred in 13% of patients. In a phase-I study in 25 RCC patients the final dose was 140 mg in 5 patients and 100 mg in 6 patients [72]. Even with patients that required dose reduction from the 140 mg level, the median average daily dose was 75.5 mg, which is higher than the currently recommended starting dose. This suggests that dose escalation may be necessary to provide maximal benefit in some patients.

These data for Cabozantinib are analogous to the data presented above for sunitinib, axitinib and pazopanib with high inter individual variability in pharmacokinetics and the impact this can have on both toxicity and clinical activity. Individualized dosing based on toxicity may reduce the need for dose reductions and drug discontinuations. Allowing patients to maintain a higher dose, by giving them treatments breaks before reducing the dose, may improve drug exposure and improve outcome for each

individual patient. This has not been formally tested for Cabozantinib.

SORAFENIB

This drug has become an orphan in the therapy of mRCC but the available data are consistent with what's been presented above for other VEGFR-TKIs. Sorafenib can be safely escalated to 600 mg BID and then 800 mg BID in a subgroup of patients [73–75]. In 43 patients that progresses on 400 mg BID dose, escalation to 600 mg BID was associated with a response in 41.9% and a median added PFS of 3.6 months [76]. In a prospective dose escalation trial of treatment naïve mRCC patients [77], the PFS was 7.4 months (95% CI, 6.3–12) for 67 evaluable patients, with a PFS of 3.7 months (95% CI, 1.8–9.7), 7.4 months (95% CI, 6.3–12), and 8.5 months (95% CI, 5.6–15) for the 400 (25 pts), 600 (12 pts), and 800 mg BID (20 pts) groups respectively, who received these doses for the longest period of time. Tumor shrinkage was similar across the 3 dose groups (72%, 75%, and 85% for the 400, 600, and 800 mg bid, respectively). While the PFS seemed higher for the dose-escalated patient, this study had too few patients for this to be statistically significant.

DISCUSSION

The concept of individualized dosing, that has now been studied prospectively for sunitinib and axitinib, challenges the use of a rigid dosing schedules for oral VEGFR-TKIs. The limited available pill strengths for oral VEGFR-TKIs and the intent to treat patient continuously lead to limited dosing options and significant dose reductions for toxicity that may reduce efficacy. Individualizing the number of days on therapy, based on toxicity, before changing the dose allows more detailed dosing.

Dose reductions and drug discontinuations are more frequent for oral drugs than intravenous drugs [78]. Oncologists individualize the dose of intravenous cancer therapy on a daily basis but usually only to reduce the dose due to toxicity. Patient with minimal toxicity are rarely dose escalated. Intravenous therapy allows much more detailed changes in dosing than is possible with oral VEGFR-TKIs. Dose individualization based on toxicity is therefore not a new concept in oncology, but until recently, has not been used for oral VEGFR-TKIs.

Contrary to the dosing recommendations for sunitinib, other VEGFR-TKIs used in mRCC are given continuously without breaks. Based on the data presented, a non-continuous toxicity driven individualized schedule as studied for sunitinib [2] and axitinib [52] may prove beneficial for patients receiving pazopanib, cabozantinib and sorafenib.

VEGFR-TKIs are here to stay as therapy for mRCC both in combination with immunotherapy [46, 79] and for all patients that are refractory to immunotherapy [80]. How to best give these drugs alone or in combination with immunotherapy remains an important research question. It's clear from the data presented that optimal drug exposure based on toxicity may improve patient outcomes and that one dose or schedule does not fit all patients.

The data presented for axitininb [56] and pazopanib [13] in the adjuvant setting show that optimal drug exposure may be just as important for this group of patients [65]. The negative results published to date for VEGFR-TKIs given in the adjuvant setting may be partly due to under dosing. In the ASSURE trial [81] the starting dose for sunitinib was reduced to 37.5 mg because of toxicity and discontinuations and a further dose reduction to 25 mg was allowed. In the S-Track trial [82], that did show a DFS benefit at one year, all patients started at the 50 mg dose and dose reductions were only allowed to 37.5 mg. All of these trials were handicapped by the rigid dosing schedules for the drugs tested that are clearly not optimal for all patients.

The 2/1 dosing schedule for sunitinib is commonly used. A population pharmacokinetic/pharmacodynamic modeling by dosing schedule based on 10 mRCC and GIST trials predicted that a 2/1 schedule vs. a 4/2 schedule for sunitinib would be as efficacious but associated with less toxicity [83]. European RCC opinion leaders did a critical review in 2017 of published data on the 2/1 schedule including 3 database studies [29, 84, 85] and one small prospective trial (total of 749 pts) [86]. Eight published reports were excluded because of methodological issues. They concluded that while the 2/1 schedule improves tolerability compared to the 4/2 schedule it was not possible to draw any conclusions about efficacy. They suggested patient should initiate therapy with the 4/2 schedule and only be switched to the 2/1 if the developed dose limiting toxicity during week 3-4 on the 4/2 schedule. A variation on the theme for the 2/1 schedule was used in a recent study in 59 patients. Before dose reduction on the 2/1 schedule the same dose was given one week on and 3 days

off alternating with 1 week on and 4 days off [87]. The primary endpoint of decreased grade-3 toxicity was not met but this schedule had a good clinical activity with a 57% ORR and PFS of 13.7 months.

An ongoing phase-II trial (NCT02689167) is comparing three different schedules for sunitinib. Patients that do not tolerate the 50 mg 4/2 schedule will be randomized to either a dose reduction to 37.5 mg on the 4/2 schedule or to a 50 mg dose on the 2/1 schedule. Based on the dose/schedule distribution (Table 2) in the sunitinib individualization study, the 2/1 schedule was optimal in only 31/88 (35.2%) of patients. Replacing one rigid schedule (4/2) with another (2/1) would have led to under-dosing in 64.8% of patients that could have either taken drug for more than 14 days or where dose was reduced rather than taking drug for less than 14 days. This does not consider the 18% of patients that could be dose escalated.

VEGFR-TKIs will continue to be an important component of therapy for most mRCC patients. The data presented above suggest that toxicity driven changes in dose and schedule are safe and can be used to manage toxicity and to optimize drug exposure for each individual patient. Individualizing the number of days on therapy, based on toxicity, with planned breaks before changing the dose allows more detailed dosing than continuous dosing. This scheduling method for VEGFR-TKIs may improve outcomes both in the metastatic and adjuvant setting. Furthermore, this scheduling method should be studied in combination with immunotherapy where overlapping toxicity may be challenging.

ACKNOWLEDGMENTS

The authors have no acknowledgements.

CONFLICT OF INTERESTS

Ambika Parmar has no conflicts to report.

Georg A Bjarnason: Honoraria for talks and advisory boards: Pfizer, Novartis, Bristol-Myers Squibb, Eisai, Ipsen. Research Funding: Pfizer, Novartis, Travel funding: Pfizer, Novartis.

REFERENCES

[1] Ratain MJ. Flushing oral oncology drugs down the toilet. J Clin Oncol. 2011;29(30):3958-9. 10.1200/JCO.2011.37.1617

[2] Bjarnason GA, Knox JJ, Kollmannsberger CK, Soulieres D, Ernst DS, Zalewski P, et al. The efficacy and safety of sunitinib given on an individualised schedule as first-line therapy for metastatic renal cell carcinoma: A phase 2 clinical trial. Eur J Cancer. 2019;108:69-77. 10.1016/j.ejca.2018.12.006

[3] Faivre S, Delbaldo C, Vera K, Robert C, Lozahic S, Lassau N, et al. Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. Journal of clinical oncology : Official journal of the American Society of Clinical Oncology. 2006;24(1):25-35. 10.1200/JCO.2005.02.2194

[4] Narjoz C, Cessot A, Thomas-Schoemann A, Golmard JL, Huillard O, Boudou-Rouquette P, et al. Role of the lean body mass and of pharmacogenetic variants on the pharmacokinetics and pharmacodynamics of sunitinib in cancer patients. Invest New Drugs. 2015;33(1):257-68. 10.1007/s10637-014-0178-2

[5] Mizuno T, Fukudo M, Terada T, Kamba T, Nakamura E, Ogawa O, et al. Impact of genetic variation in breast cancer resistance protein (BCRP/ABCG2) on sunitinib pharmacokinetics. Drug Metab Pharmacokinet. 2012;27(6):631-9.

[6] Miura Y, Imamura CK, Fukunaga K, Katsuyama Y, Suyama K, Okaneya T, et al. Sunitinib-induced severe toxicities in a Japanese patient with the ABCG2 421 AA genotype. BMC Cancer. 2014;14:964. 10.1186/1471-2407-14-964

[7] Mizuno T, Terada T, Kamba T, Fukudo M, Katsura T, Nakamura E, et al. ABCG2 421C>A polymorphism and high exposure of sunitinib in a patient with renal cell carcinoma. Ann Oncol. 2010;21(6):1382-3. 10.1093/annonc/mdq150

[8] Diekstra MH, Klumpen HJ, Lolkema MP, Yu H, Kloth JS, Gelderblom H, et al. Association analysis of genetic polymorphisms in genes related to sunitinib pharmacokinetics, specifically clearance of sunitinib and SU12662. Clin Pharmacol Ther. 2014;96(1):81-9. 10.1038/clpt.2014.47

[9] Houk BE, Bello CL, Poland B, Rosen LS, Demetri GD, Motzer RJ. Relationship between exposure to sunitinib and efficacy and tolerability endpoints in patients with cancer: Results of a pharmacokinetic/pharmacodynamic meta-analysis. Cancer Chemother Pharmacol. 2010;66(2):357-71. 10.1007/s00280-009-1170-y

[10] Motzer RJ, Hutson TE, Olsen MR, Hudes GR, Burke JM, Edenfield WJ, et al. Randomized phase II trial of sunitinib on an intermittent versus continuous dosing schedule as first-line therapy for advanced renal cell carcinoma. J Clin Oncol. 2012;30(12):1371-7. 10.1200/JCO.2011.36.4133

[11] Khosravan R, Huang X, Wiltshire R, Lechuga M, Motzer R. A retrospective analysis of data from two trials of sunitinib in patients with advanced renal cell carcinoma: Pitfalls of efficacy subgroup analyses based on dose-reduction status. J Clin Oncol. 2012;30:suppl 5; abstract 363.

[12] Rini BI, Garrett M, Poland B, Dutcher JP, Rixe O, Wilding G, et al. Axitinib in metastatic renal cell carcinoma: Results of a pharmacokinetic and pharmacodynamic analysis. J Clin Pharmacol. 2013;53(5):491-504. 10.1002/jcph.73

[13] Sternberg CN, Donskov F, Haas NB, Doehn C, Russo P, Elmeliegy M, et al. Pazopanib Exposure Relationship with Clinical Efficacy and Safety in the Adjuvant Treatment of Advanced Renal Cell Carcinoma. Clin Cancer Res. 2018;24(13):3005-3013. 10.1158/1078-0432.CCR-17-2652

[14] Gotink KJ, Broxterman HJ, Labots M, de Haas RR, Dekker H, Honeywell RJ, et al. Lysosomal sequestration of sunitinib: A novel mechanism of drug resistance. Clin Cancer Res. 2011;17(23):7337-46. 10.1158/1078-0432.CCR-11-1667

[15] Boudou-Rouquette P, Ropert S, Mir O, Coriat R, Billemont B, Tod M, et al. Variability of sorafenib toxicity and exposure over time: A pharmacokinetic/pharmacodynamic analysis. Oncologist. 2012;17(9):1204-12. 10.1634/theoncologist.2011-0439

[16] Arrondeau J, Mir O, Boudou-Rouquette P, Coriat R, Ropert S, Dumas G, et al. Sorafenib exposure decreases over time in patients with hepatocellular carcinoma. Invest New Drugs. 2012;30(5):2046-9. 10.1007/s10637-011-9764-8

[17] de Wit D, van Erp NP, den Hartigh J, Wolterbeek R, den Hollander-van Deursen M, Labots M, et al. Therapeutic drug monitoring to individualize the dosing of pazopanib: A pharmacokinetic feasibility study. Ther Drug Monit. 2015;37(3):331-8. 10.1097/FTD.0000000000000141

[18] Verheijen RB, Beijnen JH, Schellens JHM, Huitema ADR, Steeghs N. Clinical Pharmacokinetics and Pharmacodynamics of Pazopanib: Towards Optimized Dosing. Clin Pharmacokinet. 2017;56(9):987-997. 10.1007/s40262-017-0510-z

[19] Zhang L, Bhasin M, Schor-Bardach R, Wang X, Collins MP, Panka D, et al. Resistance of renal cell carcinoma to sorafenib is mediated by potentially reversible gene expression. PLoS One. 2011;6(4):e19144. 10.1371/journal.pone.0019144

[20] Wang X, Zhang L, Goldberg SN, Bhasin M, Brown V, Alsop DC, et al. High dose intermittent sorafenib shows improved efficacy over conventional continuous dose in renal cell carcinoma. J Transl Med. 2011;9:220. 10.1186/1479-5876-9-220

[21] Rini BI. Sunitinib. Expert Opin Pharmacother. 2007;8(14):2359-69. 10.1517/14656566.8.14.2359

[22] Bjarnason GA, Khalil B, Hudson JM, Williams R, Milot LM, Atri M, et al. Outcomes in patients with metastatic renal cell cancer treated with individualized sunitinib therapy: Correlation with dynamic microbubble ultrasound data and review of the literature. Urol Oncol. 2014;32(4):480-7. 10.1016/j.urolonc.2013.10.004

[23] Mancuso MR, Davis R, Norberg SM, O'Brien S, Sennino B, Nakahara T, et al. Rapid vascular regrowth in tumors after reversal of VEGF inhibition. J Clin Invest. 2006;116(10):2610-21. 10.1172/JCI24612

[24] Griffioen AW, Mans LA, de Graaf AM, Nowak-Sliwinska P, de Hoog CL, de Jong TA, et al. Rapid angiogenesis onset after discontinuation of sunitinib treatment of renal cell carcinoma patients. Clin Cancer Res. 2012;18(14):3961-71. 10.1158/1078-0432.CCR-12-0002

[25] Powles T, Kayani I, Sharpe K, Lim L, Peters J, Stewart GD, et al. A prospective evaluation of VEGF-targeted treatment cessation in metastatic clear cell renal cancer. Ann Oncol. 2013;24(8):2098-103. 10.1093/annonc/mdt130

[26] Ravaud A, Schmidinger M. Clinical biomarkers of response in advanced renal cell carcinoma. Ann Oncol. 2013;24(12):2935-42. 10.1093/annonc/mdt288

[27] Liu Y, Zhou L, Chen Y, Liao B, Ye D, Wang K, et al. Hypertension as a prognostic factor in metastatic renal cell carcinoma treated with tyrosine kinase inhibitors: A systematic review and meta-analysis. BMC Urol. 2019;19(1):49. 10.1186/s12894-019-0481-5

[28] Wang Y, Choueiri TK, Lee JL, Tan MH, Rha SY, North SA, et al. Anti-VEGF therapy in mRCC: Differences between Asian and non-Asian patients. Br J Cancer. 2014;110(6):1433-7. 10.1038/bjc.2014.28

[29] Atkinson BJ, Kalra S, Wang X, Bathala T, Corn P, Tannir NM, et al. Clinical Outcomes for Patients with Metastatic Renal Cell Carcinoma Treated with Alternative Sunitinib Schedules. J Urol. 2013;191:611-618. 10.1016/j.juro.2013.08.090

[30] Boegemann M, Hubbe M, Thomaidou D, Blackburn S, Bent-Ennakhil N, Wood R, et al. Treatment modification with sunitinib in first-line (1L) metastatic renal cell carcinoma (mRCC): An analysis of the STAR-TOR registry. Journal of Clinical Oncology. 2018;36(6_suppl):602-602. 10.1200/JCO.2018.36.6_suppl.602

[31] Porta C, Levy A, Hawkins R, Castellano D, Bellmunt J, Nathan P, et al. Impact of adverse events, treatment modifications, and dose intensity on survival among patients with advanced renal cell carcinoma treated with first-line sunitinib: A medical chart review across ten centers in five European countries. Cancer Med. 2014;3(6):1517-26. 10.1002/cam4.302

[32] Iacovelli R, Cossu Rocca M, Galli L, De Giorgi U, Sabbatini R, Santoni M, et al. Clinical outcome of patients who reduced sunitinib or pazopanib during first-line treatment for advanced kidney cancer. Urol Oncol. 2017;35(9):541 e7-541 e13. 10.1016/j.urolonc.2017.05.007

[33] Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009;27(22):3584-90. 10.1200/JCO.2008.20.1293

[34] Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med. 2013;369(8):722-31. 10.1056/NEJMoa1303989

[35] Sternberg CN, Motzer RJ, Hutson TE, Choueiri TK, Kollmannsberger C, Bjarnason GA, et al. COMPARZ Post Hoc Analysis: Characterizing Pazopanib Responders with Advanced Renal Cell Carcinoma. Clinical Genitourinary Cancer. 2019;in press.

[36] Adelaiye R, Ciamporcero E, Miles KM, Sotomayor P, Bard J, Tsompana M, et al. Sunitinib dose escalation overcomes transient resistance in clear cell renal cell carcinoma and is associated with epigenetic modifications. Mol Cancer Ther. 2015;14(2):513-22. 10.1158/1535-7163.MCT-14-0208

[37] Raphael J, Thawer A, Bjarnason GA. Sunitinib dose-escalation after disease progression in metastatic renal cell carcinoma. Urol Oncol. 2018;36(1):12 e1-12 e6. 10.1016/j.urolonc.2017.09.004

[38] Mitchell N, Fong PC, Broom RJ. Clinical experience with sunitinib dose escalation in metastatic renal cell carcinoma. Asia Pac J Clin Oncol. 2015;11(3):e1-5. 10.1111/ajco.12296

[39] Shi HZ, Tian J, Chen X, Wang D, Li CL. Clinical Experience of Escalated Sunitinib Dose in Select Patients With Metastatic Renal Cell Carcinoma. Clin Genitourin Cancer. 2017;15(1):139-144. 10.1016/j.clgc.2016.05.007

[40] Hutson TE, Lesovoy V, Al-Shukri S, Stus VP, Lipatov ON, Bair AH, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: A randomised open-label phase 3 trial. Lancet Oncol. 2013;14(13):1287-94. 10.1016/S1470-2045(13)70465-0

[41] Choueiri TK, Hessel C, Halabi S, Sanford B, Michaelson MD, Hahn O, et al. Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203 CABOSUN randomised trial): Progression-free survival by independent review and overall survival update. Eur J Cancer. 2018;94:115-125. 10.1016/j.ejca.2018.02.012

[42] Motzer RJ, Tannir NM, McDermott DF, Frontera OA, Melichar B, Choueiri TK, et al. Nivolumab plus Ipilimumab

versus Sunitinib in Advanced Renal-Cell Carcinoma. New England Journal of Medicine. 2018;DOI 10.1056/NEJMoa1712126. 10.1056/NEJMoa1712126

[43] Sabanathan D, Zhang A, Fox P, Coulter S, Gebski V, Balakrishnar B, et al. Dose individualization of sunitinib in metastatic renal cell cancer: Toxicity-adjusted dose or therapeutic drug monitoring. Cancer Chemother Pharmacol. 2017;80(2):385-393. 10.1007/s00280-017-3362-1

[44] Basappa N, Lalani ALH, Kalirai A, Wood L, Kollmannsberger C, Sim HW, et al. Individualized treatment with sunitinib versus standard dosing with sunitinib or pazopanib in patients with metastatic renal cell carcinoma: Results from the Canadian Kidney Cancer information system (CKCis). J Clin Oncol. 2017;35(6S):abstract 468.

[45] Rini BI, Escudier B, Tomczak P, Kaprin A, Szczylik C, Hutson TE, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): A randomised phase 3 trial. Lancet. 2011;378(9807):1931-9. 10.1016/S0140-6736(11)61613-9

[46] Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019;380(12):1116-1127. 10.1056/NEJMoa1816714

[47] Igarashi R, Inoue T, Fujiyama N, Tsuchiya N, Numakura K, Kagaya H, et al. Contribution of UGT1A1 genetic polymorphisms related to axitinib pharmacokinetics to safety and efficacy in patients with renal cell carcinoma. Med Oncol. 2018;35(4):51. 10.1007/s12032-018-1113-8

[48] Liu G, Rugo HS, Wilding G, McShane TM, Evelhoch JL, Ng C, et al. Dynamic contrast-enhanced magnetic resonance imaging as a pharmacodynamic measure of response after acute dosing of AG-013736, an oral angiogenesis inhibitor, in patients with advanced solid tumors: Results from a phase I study. J Clin Oncol. 2005;23(24):5464-73. 10.1200/JCO.2005.04.143

[49] Rini BI, Gruenwald V, Fishman MN, Melichar B, Ueda T, Bair AH, et al. Axitinib with or without dose titration for first-line metastatic renal cell carcinoma (mRCC): Unblinded results from a randomized phase II study. ASCO Meeting Abstracts. 2013;31(Suppl 6):Abstract 349.

[50] Rini BI, Tomita Y, Melichar B, Ueda T, Grunwald V, Fishman MN, et al. Overall Survival Analysis From a Randomized Phase II Study of Axitinib With or Without Dose Titration in First-Line Metastatic Renal Cell Carcinoma. Clin Genitourin Cancer. 2016;14(6):499-503. 10.1016/j.clgc.2016.04.005

[51] Rini BI, Schiller JH, Fruehauf JP, Cohen EE, Tarazi JC, Rosbrook B, et al. Diastolic blood pressure as a biomarker of axitinib efficacy in solid tumors. Clin Cancer Res. 2011;17(11):3841-9. 10.1158/1078-0432.CCR-10-2806

[52] Ornstein MC, Pal SK, Wood LS, Tomer JM, Hobbs BP, Jia XS, et al. Individualised axitinib regimen for patients with metastatic renal cell carcinoma after treatment with checkpoint inhibitors: A multicentre, single-arm, phase 2 study. Lancet Oncol. 2019;20(10):1386-1394. 10.1016/S1470-2045(19)30513-3

[53] Albiges L, Fay AP, Xie W, Krajewski K, McDermott DF, Heng DY, et al. Efficacy of targeted therapies after PD-1/PD-L1 blockade in metastatic renal cell carcinoma. Eur J Cancer. 2015;51(17):2580-6. 10.1016/j.ejca.2015.08.017

[54] Nadal R, Amin A, Geynisman DM, Voss MH, Weinstock M, Doyle J, et al. Safety and clinical activity of vascular endothelial growth factor receptor (VEGFR)-tyrosine kinase inhibitors after programmed cell death 1 inhibitor treatment in patients with metastatic clear cell renal cell carcinoma. Ann Oncol. 2016;27(7):1304-11. 10.1093/annonc/mdw160

[55] Motzer RJ, Escudier B, Tomczak P, Hutson TE, Michaelson MD, Negrier S, 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(6):552-62. 10.1016/S1470-2045(13)70093-7

[56] Quinn DI, Kwon TG, Eto M, Ye D, Miyake H, Seo SI, et al. Adjuvant axitinib dose modification in renal cell carcinoma (RCC): Analysis of the ATLAS study. J Clin Oncol. 2019;37:suppl; abstr 4573.

[57] Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: Results of a randomized phase III trial. J Clin Oncol. 2010;28(6):1061-8. 10.1200/JCO.2009.23.9764

[58] Deng Y, Sychterz C, Suttle AB, Dar MM, Bershas D, Negash K, et al. Bioavailability, metabolism and disposition of oral pazopanib in patients with advanced cancer. Xenobiotica. 2013;43(5):443-53. 10.3109/00498254.2012.734642

[59] Imbs DC, Negrier S, Cassier P, Hollebecque A, Varga A, Blanc E, et al. Pharmacokinetics of pazopanib administered in combination with bevacizumab. Cancer Chemother Pharmacol. 2014;73(6):1189-96. 10.1007/s00280-014-2455-3

[60] Hurwitz HI, Dowlati A, Saini S, Savage S, Suttle AB, Gibson DM, et al. Phase I trial of pazopanib in patients with advanced cancer. Clin Cancer Res. 2009;15(12):4220-7. 10.1158/1078-0432.CCR-08-2740

[61] Verheijen RB, Bins S, Mathijssen RH, Lolkema MP, van Doorn L, Schellens JH, et al. Individualized Pazopanib Dosing: A Prospective Feasibility Study in Cancer Patients. Clin Cancer Res. 2016;22(23):5738-5746. 10.1158/1078-0432.CCR-16-1255

[62] Suttle AB, Ball HA, Molimard M, Hutson TE, Carpenter C, Rajagopalan D, et al. Relationships between pazopanib exposure and clinical safety and efficacy in patients with advanced renal cell carcinoma. Br J Cancer. 2014;111(10):1909-16. 10.1038/bjc.2014.503

[63] Hutson TE, Davis ID, Machiels JP, De Souza PL, Rottey S, Hong BF, et al. Efficacy and safety of pazopanib in patients with metastatic renal cell carcinoma. J Clin Oncol. 2010;28(3):475-80. 10.1200/JCO.2008.21.6994

[64] Motzer RJ, Haas NB, Donskov F, Gross-Goupil M, Varlamov S, Kopyltsov E, et al. Randomized Phase III Trial of Adjuvant Pazopanib Versus Placebo After Nephrectomy in Patients With Localized or Locally Advanced Renal Cell Carcinoma. J Clin Oncol. 2017;35(35):3916-3923. 10.1200/JCO.2017.73.5324

[65] Rini BI. Goldilocks Dosing of TKIs: A Dose that Is Just Right Leads to Optimal Outcomes. Clin Cancer Res. 2018;24(13):2979-2980. 10.1158/1078-0432.CCR-18-0291

[66] Choueiri TK, Escudier B, Powles T, Tannir NM, Mainwaring PN, Rini BI, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): Final results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2016;17(7):917-927. 10.1016/S1470-2045(16)30107-3

[67] Choueiri TK, Escudier B, Powles T, Mainwaring PN, Rini BI, Donskov F, et al. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015;373(19):1814-23. 10.1056/NEJMoa1510016

[68] Lacy S, Hutmacher MM, Yang B, Motzer RJ, Escudier BJ, Powles T, et al. Cabozantinib (C) exposure-response (ER) modeling of safety endpoints in patients (pts) with renal cell

carcinoma (RCC) in the phase III METEOR study. J Clin Oncol. 2017;35(suppl 6):ASCO GU 2017 abstract 447.

[69] Lacy SA, Miles DR, Nguyen LT. Clinical Pharmacokinetics and Pharmacodynamics of Cabozantinib. Clin Pharmacokinet. 2017;56(5):477-491. 10.1007/s40262-016-0461-9

[70] Jonasch E, Motzer RJ, Escudier B, Powles T, Markby DW, Nielsen J, et al. Cabozantinib (C) exposure-response (ER) modeling of efficacy and safety endpoints as a function of clearance in patients (pts) with renal cell carcinoma (RCC). J Clin Oncol. 2018;36(suppl 6S;):ASCO-GU 2018 abstr 645.

[71] Motzer RJ, Escudier B, Powles T, Scheffold C, Choueiri TK. Long-term follow-up of overall survival for cabozantinib versus everolimus in advanced renal cell carcinoma. Br J Cancer. 2018. 10.1038/s41416-018-0061-6

[72] Choueiri TK, Pal SK, McDermott DF, Morrissey S, Ferguson KC, Holland J, et al. A phase I study of cabozantinib (XL184) in patients with renal cell cancer. Ann Oncol. 2014;25(8):1603-8. 10.1093/annonc/mdu184

[73] Amato R, Zhai J, Willis J, Saxena S, DeFoe M. A phase II trial of intrapatient dose-escalated sorafenib in patients with metastatic renal cell carcinoma. Clin Genitourin Cancer. 2012;10(3):153-8. 10.1016/j.clgc.2012.03.001

[74] Mancuso A, Di Paola ED, Leone A, Catalano A, Calabro F, Cerbone L, et al. Phase II escalation study of sorafenib in patients with metastatic renal cell carcinoma who have been previously treated with anti-angiogenic treatment. BJU Int. 2012;109(2):200-6. 10.1111/j.1464-410X.2011.10421.x

[75] Strumberg D, Richly H, Hilger RA, Schleucher N, Korfee S, Tewes M, et al. Phase I clinical and pharmacokinetic study of the Novel Raf kinase and vascular endothelial growth factor receptor inhibitor BAY 43-9006 in patients with advanced refractory solid tumors. J Clin Oncol. 2005;23(5):965-72. 10.1200/JCO.2005.06.124

[76] Escudier B, Szczylik C, Hutson TE, Demkow T, Staehler M, Rolland F, et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon Alfa-2a in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009;27(8):1280-9. JCO.2008.19.3342 [pii] 10.1200/JCO.2008.19.3342

[77] Gore ME, Jones RJ, Ravaud A, Kuczyk M, Demkow T, Bearz A, et al. Efficacy and safety of intrapatient dose escalation of sorafenib as first-line treatment for metastatic renal cell carcinoma (mRCC). ASCO Meeting Abstracts. 2011;29(15_suppl):4609.

[78] Prasad V, Massey PR, Fojo T. Oral anticancer drugs: How limited dosing options and dose reductions may affect outcomes in comparative trials and efficacy in patients. J Clin Oncol. 2014;32(15):1620-9. 10.1200/JCO.2013.53.0204

[79] Motzer RJ, Penkov K, Haanen J, Rini B, Albiges L, Campbell MT, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019;380(12):1103-1115. 10.1056/NEJMoa1816047

[80] Auvray M, Auclin E, Barthelemy P, Bono P, Kellokumpu-Lehtinen P, Gross-Goupil M, et al. Second-line targeted therapies after nivolumab-ipilimumab failure in metastatic renal cell carcinoma. Eur J Cancer. 2019;108:33-40. 10.1016/j.ejca.2018.11.031

[81] Haas NB, Manola J, Uzzo RG, Flaherty KT, Wood CG, Kane C, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): A double-blind, placebo-controlled, randomised, phase 3 trial. Lancet. 2016;387(10032):2008-16. 10.1016/S0140-6736(16)00559-6

[82] Ravaud A, Motzer RJ, Pandha HS, George DJ, Pantuck AJ, Patel A, et al. Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy. N Engl J Med. 2016;375(23):2246-2254. 10.1056/NEJMoa1611406

[83] Khosravan R, Motzer RJ, Fumagalli E, Rini BI. Population Pharmacokinetic/Pharmacodynamic Modeling of Sunitinib by Dosing Schedule in Patients with Advanced Renal Cell Carcinoma or Gastrointestinal Stromal Tumor. Clin Pharmacokinet. 2016;55(10):1251-69. 10.1007/s40262-016-0404-5

[84] Bracarda S, Iacovelli R, Boni L, Rizzo M, Derosa L, Rossi M, et al. Sunitinib administered on 2/1 schedule in patients with metastatic renal cell carcinoma: The RAINBOW analysis. Ann Oncol. 2015;26(10):2107-13. 10.1093/annonc/mdv315

[85] Najjar YG, Mittal K, Elson P, Wood L, Garcia JA, Dreicer R, et al. A 2 weeks on and 1 week off schedule of sunitinib is associated with decreased toxicity in metastatic renal cell carcinoma. Eur J Cancer. 2014;50(6):1084-9. 10.1016/j.ejca.2014.01.025

[86] Lee JL, Kim MK, Park I, Ahn JH, Lee DH, Ryoo HM, et al. RandomizEd phase II trial of Sunitinib four weeks on and two weeks off versus Two weeks on and One week off in metastatic clear-cell type REnal cell carcinoma: RESTORE trial. Ann Oncol. 2015;26(11):2300-5. 10.1093/annonc/mdv357

[87] Jonasch E, Slack RS, Geynisman DM, Hasanov E, Milowsky MI, Rathmell WK, et al. Phase II Study of Two Weeks on, One Week off Sunitinib Scheduling in Patients With Metastatic Renal Cell Carcinoma. J Clin Oncol. 2018;36(16):1588-1593. 10.1200/JCO.2017.77.1485