Safety and efficacy of molecularly targeted agents in patients with metastatic kidney cancer with renal dysfunction

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Multiple molecularly targeted agents (MTAs) have been approved for the management of metastatic renal cell carcinoma (mRCC). Sunitinib and mammalian target of rapamycin inhibitors (temsirolimus, everolimus) are primarily metabolized in the liver, whereas the metabolism of bevacizumab is unclear. There are limited data on the toxicity profile and the efficacy of these agents in patients with renal insufficiency (RI). This is clinically relevant, especially as about one-third of patients with mRCC have renal dysfunction. The primary objective was to assess the safety and efficacy of targeted agents in patients with mRCC with RI. Medical records of patients with mRCC at Wayne State University, started on sunitinib, temsirolimus, everolimus, or bevacizumab, were reviewed. Patients with a calculated creatinine clearance of less than or equal to 60 ml/min were deemed to have RI. Data on safety and efficacy of MTA therapy were collected and analyzed with respect to renal function. RI was observed in 33% of our patients with mRCC. The incidence of toxicities, responses, time to progression, and overall survival were not significantly different in patients with RI compared with patients with normal renal function. Patients with RI had larger median increases in blood pressure with sunitinib and bevacizumab, increased incidence of thyroid dysfunction with sunitinib, and increased incidence of rash and dose interruptions with mammalian target of rapamycin inhibitors, than did patients with normal renal function. In conclusion, RI was commonly observed in our patients with mRCC. Molecularly targeted agents are well tolerated, and efficacy seems to be maintained in patients with RI. Vigilant monitoring of hypertension would be recommended for patients receiving sunitinib and bevacizumab. *Anti-Cancer Drugs* 22:794–800 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Renal cell carcinoma (RCC) is the third most common tumor of the urinary tract and accounts for about 3.8% of all adult malignancies [1]. Approximately 58 240 new cases of RCC were diagnosed in the United States in 2010, with an estimated 13 040 deaths. More than a quarter of patients present with the advanced stage of disease and about one-third of patients undergoing resection for localized disease will have a recurrence [2]. Previously, the median survival of patients with metastatic RCC (mRCC) despite immunotherapy was 12–15 months [3]. The use of molecularly targeted agents (MTAs) revolutionized the management of mRCC with the availability of several treatment options.

The US Food and Drug Administration (FDA) has approved several MTAs for the treatment of mRCC. Sorafenib (Nexavar), in a phase III trial consisting of 903 patients pretreated with immunotherapy, was shown to significantly prolong progression-free survival (PFS) of patients with mRCC compared with placebo [4]. Sunitinib (Sutent) also improved PFS and overall survival (OS) compared with interferon-α in a 750-patient, randomized, phase III trial [5]. Temsirolimus (Torisel) improved OS and PFS in poor-risk patients with mRCC compared with interferon-α [6]. Everolimus (Afinitor) was approved for the treatment of patients with mRCC after failure of the treatment with sunitinib or sorafenib [7]. The combination of bevacizumab (Avastin) and interferon-α was approved based on evidence from a randomized, phase III study of 649 patients, showing longer PFS in patients receiving the combination, compared with those receiving interferon-α alone [8]. In a recent randomized, placebo-controlled trial, pazopanib monotherapy significantly prolonged PFS and tumor response in both treatment-naive and cytokine-pretreated patients with mRCC [9]. In summary, since 2005, a concerted effort by clinical trials has led to the successful establishment of a number of targeted therapies in RCC management.

Sorafenib is an orally administered multikinase inhibitor targeting the platelet-derived growth factor, vascular endothelial growth factor (VEGF) receptors, c-KIT, and Ras tyrosine kinases [10]. Sorafenib is metabolized primarily in the liver, undergoing oxidative metabolism mediated by CYP3A4. Sorafenib therapy has been

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extensively evaluated in mild and moderate hepatic dysfunction, with no dosage reduction recommended for patients with mild-to-moderate (Child–Pugh A–B) hepatic impairment. Sunitinib is an oral, multitargeted tyrosine kinase inhibitor of VEGFRs, platelet-derived growth factor receptors, and c-KIT [11]. Sunitinib is also metabolized primarily in the liver by hepatic enzyme cytochrome P450-3A4. Renal elimination is a minor route of excretion for sunitinib (16% of the administered dose is eliminated in urine) [12]. Bevacizumab is a monoclonal antibody targeted against the VEGF ligand, which inhibits the biological activity of VEGF. The metabolism of bevacizumab is nonspecific, with tissue distribution consistent with the disposition of a general monoclonal antibody [13]. Temsirolimus and everolimus are both inhibitors of mammalian target of rapamycin (mTOR), an intracellular protein implicated in multiple growth-related cellular functions. mTOR inhibitors are metabolized primarily in the liver by hepatic cytochrome P45-3A4. Elimination is primarily through the feces and only about 5% of the administered dose is detected in the urine [14].

Renal insufficiency (RI) is seen commonly in patients with RCC and has been reported to be as high as 50% of all cases by one group [15]. This is explained by the observation that the median age of diagnosis of RCC is 65 years [1]. With a higher incidence of diabetes and hypertension in this age group, a larger proportion of patients with RCC are likely to have underlying chronic kidney disease [10]. Nephrectomy prolongs OS in patients with mRCC [16]. As a result, a large proportion of patients with mRCC undergo nephrectomy, increasing the risk of RI [10]. Patients maintained on chronic dialysis are also at an increased risk of developing malignancies, including RCC. The incidence of RCC in these patients requiring chronic dialysis has been reported to be approximately 1–3% [17].

It is not clear, however, whether MTAs would be safe and effective in patient populations with RI. The majority of clinical trials testing these agents excluded patients with moderately impaired renal function. The exclusion criterion for the phase III trial evaluating sunitinib was serum creatinine greater than two times the normal, whereas all other clinical trials evaluating bevacizumab, temsirolimus, and everolimus excluded patients with serum creatinine greater than one and half times the upper limit of normal. It is possible that a few patients with mildly impaired renal function and estimated creatinine clearance (CrCl) between 40 and 59 ml/min might have been included in the large phase III trials, but this patient subgroup has not been well characterized in the published studies.

There have been multiple case reports of patients with an impaired renal function successfully treated with newer MTAs [18,19]. We have previously published our experience in the clinical application of sorafenib in mRCC with RI. Tolerability and comparable efficacy were observed in the patients with RI treated with sorafenib in our series [10]. In this retrospective study, we attempt to evaluate the feasibility, safety, and efficacy of other MTAs including sunitinib, bevacizumab, temsirolimus, and everolimus in patients with mRCC with RI. This will help to guide the practical management of this fairly common clinical scenario in RCC.

Materials and methods

Patient characteristics

The primary objective was to assess the safety and the efficacy of the four MTAs in patients with an impaired renal function and compare it with that observed in patients with normal renal function. The protocol was approved by the Human Investigation Committee of Wayne State University. Medical records of consecutive patients with mRCC treated with sunitinib, bevacizumab, temsirolimus, or everolimus between July 2004 and March 2010 were reviewed. According to the Modification of Diet in Renal Disease method for estimating glomerular filtration rate [20], patients with a calculated CrCl of less than or equal to 60 ml/min (chronic kidney disease stages 3, 4, or 5, as per Kidney Disease Outcomes Quality Initiatives guidelines) were deemed to have RI [21]. Data on patient demographics, safety, efficacy, and dosing of all the MTA therapy were collected and analyzed with respect to renal function. Toxicities were graded as per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Dose modifications and interruptions of targeted therapy administration were noted. The response was evaluated as per the Response Evaluation Criteria In Solid Tumors [22].

Statistical methods

Descriptive statistics were used to summarize various patient characteristics, safety, and efficacy data. Time to progression (TTP) was measured from the day of starting MTA therapy until documented disease progression or death from mRCC. TTP was censored as of the date of last tumor assessment for patients still free of progression or if a patient died of a cause other than renal cell cancer. OS was measured from the day of starting MTA therapy until death due to any cause. Patient survival data were obtained either from the patient's medical records or direct communication, or from the United States Social Security Administration Death Index. OS was censored for patients still alive as of the last date of contact for vital status determination. Follow-up and survival data are reported as of March 2010.

Standard 90% confidence limits for the response rate were calculated with the method of Clopper and Pearson. Response and toxicity rates were compared with Fisher's exact test (two sided). Standard Kaplan–Meier estimates

of the censored TTP and OS distributions were computed. Owing to the small sample sizes, survival statistics (e.g. median) were estimated more conservatively using linear interpolation among successive event times on the Kaplan–Meier curves [23].

Results

Patient characteristics

A total of 51 patients with mRCC treated with sunitinib, bevacizumab, temsirolimus, or everolimus between July 2004 and March 2010 were analyzed. Eleven of these patients were treated with more than one MTA given sequentially after the failure of the previous MTA therapy. Seventeen (33%) of the 51 study patients had RI, defined as CrCl of less than or equal to 60 ml/min. The CrCl of the patients studied ranged from 24 to 190 ml/min, with a majority (16 of 23) having mildly impaired renal function, that is, CrCl ranging between 40 and 59 ml/min. None of the patients were dialysis dependent. Five of the 11 patients (45%) receiving more than one MTA had a notable decline in their renal function before the initiation of the next line of therapy.

Detailed demographics and tumor characteristics according to the MTA received and estimated CrCl levels are summarized in Table 1. Median age in the patients with RI was higher than in the patients with normal renal function in all MTA therapy groups, with most of the patients being men. All patients treated with sunitinib and bevacizumab had a Karnofsky performance status of more than or equal to 80%. Twenty-five percent (six of 24) of patients treated with mTOR inhibitors had a Karnofsky performance status of 60–70%. Patients with both RI and normal renal function were well matched with regard to Memorial Sloan Kettering Cancer Center prognostic risk factors across all MTA therapy groups.

Toxicities

The types of toxicities observed were not significantly different in patients with RI compared with patients with normal renal function (Tables 2–4).

Predominant toxicities observed in the patients receiving sunitinib were hypertension (81%), fatigue (89%), and hand–foot syndrome (35%; Table 2). A few notable differences were that patients with RI had an increased incidence of grade 3 fatigue (85 vs. 64%) and a higher incidence of thyroid dysfunction (60%) with sunitinib therapy, compared with the patients with normal renal function (25%).

The most frequent toxicities in the patients receiving bevacizumab were hypertension (85%), fatigue (54%), and proteinuria (50%; Table 3). Predominant toxicities noted in the patients receiving the mTOR inhibitors were fatigue (83%), mucositis (46%), proteinuria (56%), hypercholesterolemia (57%), hypertriglyceridemia (64%), and hyperglycemia (50%; Table 4). Patients with RI had higher incidences of rash (45 vs. 15%) and infections (27 vs. 8%) compared with patients with normal renal function. The incidence of pulmonary toxicities (all grades), including interstitial pneumonitis, was 30% for the group, with no major differences noted depending on renal function.

Table 1 Patient characteristics according to the molecularly targeted agent received and estimated creatinine clearance

	Sunitinib		Bevacizumab		mTOR inhibitors	
Characteristics	CrCl ≤ 60 ml/min *N*=7	CrCl >60 ml/min *N*=19	CrCl ≤ 60 ml/min *N*=5	CrCl >60 ml/min *N*=8	CrCl ≤ 60 ml/min *N*=11	CrCl >60 ml/min *N*=13
Median age (years)	67	54	70	60	61	55
Sex						
Male	4	16	2	5	9	9
Female	3	3	3	3	2	4
Race						
Caucasian	6	18	3	8	6	13
African–American	1	–	2	–	2	0
Others	–	1	–	–	3	0
Previous nephrectomy (%)	6 (86)	18 (95)	5 (100)	7 (88)	10 (91)	13 (100)
KPS						
≥ 80 (%)	7 (100)	19 (100)	5 (100)	8 (100)	7 (64)	11 (85)
60–70 (%)	–	–	–	–	4 (36)	2 (15)
MSKCC score						
0–1 (%)	7 (100)	16 (84)	4 (80)	8 (100)	7 (64)	10 (77)
2 (%)	–	3 (16)	–	–	3 (27)	3 (23)
3 (%)	–	–	–	–	1 (9)	–
Histology						
Clear cell (%)	6 (86)	18 (95)	5 (100)	5 (100)	11 (100)	10 (77)
Papillary (%)	–	1 (5)	–	–	–	1 (8)
Chromophobe (%)	–	–	–	–	–	2 (15)
Others (%)	1 (14)	–	–	–	–	–
Median CrCl ml/min (range)	47 (37–55)	91 (66–190)	55 (24–56)	91 (76–100)	42 (19–59)	71 (63–120)

CrCl, creatinine clearance; KPS, Karnofsky Performance Status; MSKCC, Memorial Sloan Kettering Cancer Center score; mTOR, mammalian target of rapamycin.

Table 2 Toxicity and efficacy data of patients treated with sunitinib according to creatinine clearance

Characteristics	Sunitinib	
	CrCl $\leq$ 60 ml/min *N*=7 (%)	CrCl >60 ml/min *N*=19 (%)
Skin rash (mild–moderate) (including hand–foot syndrome)	2 (29)	7 (37)
Diarrhea (grade 1–2)	1 (14)	7 (37)
Infections	0	8 (42)
Fatigue		
Mild	0	5 (26)
Moderate	5 (71)	10 (53)
Severe	1 (14)	2 (11)
Drop in ejection fraction >15%	1/3[a] (33)	3/15[a] (20)
Decrease in CrCl	1 (14)	6 (32)
Median drop in CrCl (ml/min)	5	15
Bleeding	1 (14)	2 (11)
Thyroid dysfunction	3/5[a] (60)	2/8[a] (25)
Proteinuria	0/5[a]	6/13[a] (46)
Median SBP before starting therapy (mmHg)	146 (99–153)	143 (114–180)
Median DBP before starting therapy (mmHg)	77 (50–88)	82 (61–100)
Median rise in SBP during therapy	30 mm	18 mm
Median rise in DBP during therapy	15 mm	5 mm
Dose interruption(s)	1 (14)	6 (32)
Dose reduction(s)	0	3 (16)

CrCl, creatinine clearance; DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a]Denominator indicates the number of patients tested if fewer than the total number.

Table 3 Toxicity and efficacy data of patients treated with bevacizumab according to creatinine clearance

Characteristics	Bevacizumab	
	CrCl $\leq$ 60 ml/min *N*=5 (%)	CrCl >60 ml/min *N*=8 (%)
Skin rash (mild–moderate)	1 (20)	1 (13)
Diarrhea (grade 1–2)	0	1 (13)
Infections	1 (20)	5 (63)
Fatigue		
Mild	0	4 (50)
Moderate	2 (40)	3 (38)
Severe	1 (20)	1 (13)
Proteinuria	2 (40)	4 (50)
Bleeding	1 (20)	2 (25)
Gastrointestinal perforations	0	0
Arterial or venous thrombotic events	0	1 (13)
Median SBP before starting therapy (mmHg)	131 (103–143)	144 (106–183)
Median DBP before starting therapy (mmHg)	64 (50–80)	83 (60–90)
Median rise in SBP during therapy	42 mm	21 mm
Median rise in DBP during therapy	18 mm	12 mm
Dose interruption(s)	3 (60)	5 (63)
Dose reduction(s)	1 (20)	3 (37)

CrCl, creatinine clearance; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Hypertension

Hypertension is a class-effect toxicity seen with VEGF-inhibition therapy. An increase in the blood pressure is commonly observed in patients receiving sunitinib or bevacizumab. Of the 26 patients receiving sunitinib, 16 patients (61%) had baseline hypertension [systolic blood pressure (SBP) $\geq$ 140 and/or diastolic blood pressure (DBP) $\geq$ 90], including four patients with RI and 12 with normal renal function. All patients with RI had an increase in their SBP and DBP readings on therapy. Median increase in both SBP and DBP was higher in the RI group compared with patients with normal kidney function (Tables 2 and 3).

Six patients (46%) receiving bevacizumab had hypertension at baseline, including two with RI and four with normal renal function. Almost all patients (85%) had an increase in their SBP and DBP readings on therapy, irrespective of their renal function. Median elevations in SBP and DBP were higher in patients with RI. One patient with renal dysfunction was hospitalized for severe uncontrolled hypertension.

Dose interruptions and dose adjustments

All patients were started on the FDA-approved starting doses of sunitinib, bevacizumab, temsirolimus, and everolimus, and these MTAs seemed to be well tolerated in patients with RI as well as in patients with normal renal function. There were no observed increases in the number of dose interruptions or dose adjustments in the RI group compared with the renal-sufficient group receiving either sunitinib or bevacizumab (Tables 2 and 3). Patients with RI receiving the mTOR inhibitors had a higher incidence of dose interruptions (64%) than the patients with normal renal function (38%), although the number of patients requiring dose reductions was similar in both groups (Table 4).

Response and survival

Patients with RI receiving sunitinib, bevacizumab, temsirolimus, or everolimus demonstrated comparable response rates, TTP, and OS as observed in their counterparts with normal renal function (Table 5). Clinical benefit rates (clinical benefit rate = partial response + stable disease) were 57 versus 47% with sunitinib, 80 versus 63% with bevacizumab, and 70 versus 53% with mTOR inhibitors in patients with RI versus normal renal function, respectively.

Median TTP was 2.7 versus 2.8 months with sunitinib, 6.2 versus 3.7 months with bevacizumab, and 8.3 versus 2.3 months with mTOR inhibitors in patients with RI versus normal renal function, respectively. Median OS was 13.2 versus 8 months with sunitinib, 28.8 versus 11.4 months with bevacizumab, and 12.5 versus 6.2 months with mTOR inhibitors in patients with RI versus normal renal function, respectively.

Discussion

In our study, RI defined as CrCl of less than or equal to 60 ml/min was seen in 37% of patients with RCC, consistent with rates previously reported in the literature [15].

The CrCl of the patients with RI ranged from 24 to 59 ml/min and a majority of our patients with RI (16 of 23) had mildly impaired renal function, with none of the patients being dialysis dependent. As would be expected, the patients with RI were older than the patients with normal renal function. Chronic kidney disease is frequent in this group possibly because of underlying age-related medical problems such as diabetes or hypertension, besides the history of previous nephrectomies.

Table 4 Toxicity and efficacy data of patients treated with mammalian target of rapamycin inhibitors (temsirolimus and/or everolimus) according to creatinine clearance

	mTOR inhibitors	
Characteristics	CrCl $\leq$ 60 ml/min $N=11$ (%)	CrCl $>$60 ml/min $N=13$ (%)
Skin rash (mild–moderate)	5 (45)	2 (15)
Diarrhea (grade 1–2)	1 (9)	2 (15)
Infections	3 (27)	1 (8)
Fatigue		
Mild	6 (55)	9 (69)
Moderate	3 (27)	2 (15)
Severe	0	0
Proteinuria	7 (64)	6/12[a] (50)
Mucositis	4 (36)	7 (54)
Pulmonary toxicity	4 (36)	3 (23)
Hypercholesterolemia		
Grade 1	1/7[a] (14)	2/7[a] (29)
Grade 2	2/7[a] (29)	3/7[a] (43)
Hypertriglyceridemia		
Grade 1	1/7[a] (14)	3/7[a] (43)
Grade 2	2/7[a] (29)	1/7[a] (14)
Grade 3	1/7[a] (14)	1/7[a] (14)
Hypercholesterolemia/ hypertriglyceridemia requiring treatment	3/9[a] (33)	3/12[a] (25)
Hyperglycemia		
Grade 1	3/7[a] (43)	1/7[a] (14)
Grade 2	1/7[a] (14)	2/7[a] (29)
Hyperglycemia requiring treatment	3/9[a] (33)	1/12[a] (8)
Dose interruption(s)	7 (64)	5 (38)
Dose reduction(s)	3 (27)	3 (23)

CrCl, creatinine clearance; mTOR, mammalian target of rapamycin.
[a]Denominator indicates the number of patients tested if less than the total number.

Multiple-targeted therapies have now been FDA approved for use in mRCC. Although the large randomized clinical trials evaluating these drugs might have included a few patients with mildly impaired CrCl the outcomes of this subgroup of patients have not been well characterized. There are minimal data regarding safety and efficacy of the use of MTAs in patients with mRCC with RI compared with patients with normal renal function. There have been multiple case reports in the literature of patients with RI being successfully treated with these newer agents [18,19]. Most of these case reports do not report on the toxicities peculiar to these MTAs in great detail. Our group recently reported on safety and efficacy of using sorafenib in patients with RI [10]. Such patients had a higher incidence of diarrhea, hand–foot syndrome, and dose reductions/interruptions than patients with normal renal function, with no noted difference in response rates, PFS, or OS.

There are reports in the literature describing clinical experience with sunitinib in patients with renal dysfunction. Khosravan *et al.* [24] reported on the pharmacokinetics of a single dose of 50 mg of sunitinib in patients with severe RI or end-stage renal disease (ESRD). The pharmacokinetics of sunitinib in patients with severe RI seemed to be similar to those with normal renal function. Plasma exposure to sunitinib and its metabolites seemed to be lower in patients with ESRD compared with the individuals with normal or severe RI. As this tested only a single dose of sunitinib, no definite conclusions on cumulative toxicities, clinical outcomes, and acute toxicities can be drawn to help guide clinical decisions in practice. Josephs *et al.* [25] reported on 21 patients from five institutions with CrCl of less than 30 ml/min or ESRD treated with sunitinib. Their experience suggested that patients treated with sunitinib with severe RI or ESRD on hemodialysis have PFS comparable with patients with normal renal function. In addition, sunitinib seemed to be reasonably well tolerated in this group of patients without any excess toxicity.

Table 5 Response rates, time to progression, and overall survival according to the molecularly targeted agent received and the estimated creatinine clearance

	Sunitinib		Bevacizumab		mTOR inhibitors	
Characteristics	CrCl $\leq$ 60 ml/min $N=7$	CrCl $>$60 ml/min $N=19$	CrCl $\leq$ 60 ml/min $N=5$	CrCl $>$60 ml/min $N=8$	CrCl $\leq$ 60 ml/min $N=11$	CrCl $>$60 ml/min $N=13$
RECIST response[a]						
CR	0	–	0	0	0	0
PR (%)	0	4 (21)	0	0	3 (30)	2 (15)
SD (%)	4 (57)	5 (26)	4 (80)	5 (63)	4 (40)	5 (38)
PD (%)	1 (14)	8 (42)	0	3 (37)	1 (10)	4 (31)
Median time to progression (months) (90% CI)	2.7 (1.6–9.6)	2.8 (2.4–4.3)	6.2 (2.4–16.4)[b]	3.7 (0.0–6.4)[b]	8.3 (0.0–9.0)	2.3 (1.6–3.9)
Median overall survival (months) (90% CI)	13.2 (1.1–27.4)	8.0 (4.4–16.3)	28.8 (0.3–29.5)	11.4 (5.1–24.2)	12.5 (7.4–21)	6.2 (3.1–8.7)

CI, confidence interval; CR, complete response; CrCl, creatinine clearance; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.
[a]Patient responses may not add up to 100% because of the few patients that are too early for evaluation.
[b]An 80% CI, due to very small number of patients treated with bevacizumab.

Overall, the frequency of toxicities noted in our patient population treated with sunitinib was comparable with the range reported in the literature, with the exception of a higher incidence of therapy-induced hypertension [26]. In addition, our study found that patients with RI had an increased incidence of higher-grade fatigue, increased thyroid dysfunction, and higher median rises in both SBP and DBP on therapy than patients with normal renal function.

There is very limited literature on the use of bevacizumab in patients with RI. As bevacizumab was approved for use much earlier in metastatic colorectal cancer than in mRCC, isolated case reports in the literature relate to the safety of bevacizumab in patients with metastatic colorectal cancer with RI [27]. Garnier-Viougeat *et al.* [28] recently reported on the pharmacokinetics of bevacizumab in a patient with mRCC on hemodialysis. They treated their patient with a reduced dose of 5 mg/kg every 2 weeks compared with the standard 10 mg/kg every 2 weeks. Bevacizumab pharmacokinetic data obtained on the off-dialysis day were similar to the reference values at steady state in patients with normal renal function treated at the standard dose. Although the bevacizumab area under the curve for the hemodialysed patient was half of the reference normal values, the bevacizumab concentrations were above the reference bevacizumab IC_{50} during the first 10 days after infusion. Bevacizumab did not seem to be dialyzable and could be administered anytime before or after hemodialysis. On account of these findings, they recommended a dose of 5 mg/kg to be used in hemodialysis-dependent patients. Toxicities or efficacy of bevacizumab was not reported. The patients in our study received the standard dose of bevacizumab at 10 mg/kg every 2 weeks, although none of them were dialysis dependent. Despite being treated at standard dose, only one patient of the five (20%) with RI required a dose reduction compared with three patients of eight (37%) with normal renal function. There were no significant differences in the toxicities on therapy with bevacizumab observed between the RI group and those with normal renal function, with the exception of higher median rises in both SBP and DBP in the RI group.

The successful use of mTOR inhibitors such as everolimus and sirolimus as immunosuppressants in cardiac, kidney, and liver transplant patients with RI has been described, although these reports do not include toxicities [29,30]. Overall, the incidences of toxicities seen in our study patients with mTOR inhibitors are consistent with those reported in the literature [26]. Patients with RI had higher incidences of rash, infections, and dose interruptions than the patients with normal renal function, with no significant difference noted in the incidence of other toxicities.

Our patients with RI receiving any of the MTAs seem to have comparable response rates, but favorable TTP and OS, than patients with normal renal function. It is unclear whether this difference is related to longer plasma exposure of the MTAs or its metabolites in patients with RI. Khosravan *et al.* [24] showed that plasma exposure to sunitinib and its metabolites appeared lower in patients with ESRD compared with the individuals with normal or severely impaired renal function. The pharmacokinetics of a single dose of sunitinib has been reported to be no different in patients with RI; however, it is possible that the kinetics of sunitinib and its metabolites may change with chronic administration. Garnier-Viougeat *et al.* [28] also reported that the bevacizumab pharmacokinetic data in a hemodialysis patient were similar to the reference values at steady state in patients with normal renal function, despite the patient being treated at a lower dose than the standard doses received by patients in our study.

In conclusion, RI is seen in about one-third of our patients with mRCC. The study conclusions are limited by the fact that a majority of the patients with RI had mildly impaired renal function (CrCl = 40–59 ml/min). Moreover, the study is a retrospective analysis of a group of highly selected patients treated at a single institution and the results should be interpreted in this light. However, it still reasonably demonstrates that the newer MTAs such as sunitinib, bevacizumab, temsirolimus, and everolimus are well tolerated at standard doses and efficacy is maintained in patients with mild-to-moderate RI. Patients with RI have greater magnitude of increases in blood pressure with sunitinib and bevacizumab, and higher incidence of thyroid dysfunction with sunitinib. Close monitoring for these specific toxicities is recommended. Our study should help guide the clinical management of patients with mRCC with RI, on targeted therapies.

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Conflicts of interest

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Conflicts of interest: all authors have no relevant conflicts of interest or financial disclosure to declare.

References

1 Cohen HT, McGovern FJ. Renal-cell carcinoma. *N Engl J Med* 2005; **353**:2477–2490.
2 Lam JS, Belldegrun AS, Pantuck AJ. Long-term outcomes of the surgical management of renal cell carcinoma. *World J Urol* 2006; **24**:255–266.
3 Coppin C, Porzsolt F, Awa A, Kumpf J, Coldman A, Wilt T. Immunotherapy for advanced renal cell cancer. *Cochrane Database Syst Rev* 2005; CD001425.
4 Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, *et al.* Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007; **356**:125–134.
5 Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, *et al.* Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007; **356**:115–124.
6 Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, *et al.* Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007; **356**:2271–2281.

7 Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, *et al.* Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2008; **372**:449–456.
8 Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szczylik C, *et al.* Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet* 2007; **370**:2103–2111.
9 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**:1061–1068.
10 Parsa V, Heilbrun L, Smith D, Sethi A, Vaishampayan U. Safety and efficacy of sorafenib therapy in patients with metastatic kidney cancer with impaired renal function. *Clin Genitourin Cancer* 2009; **7**:E10–E15.
11 Mendel DB, Laird AD, Xin X, Louie SG, Christensen JG, Li G, *et al.* In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. *Clin Cancer Res* 2003; **9**:327–337.
12 Bello CL, Patyna S, Kang P, Klamerus K. A phase I mass-balance study to evaluate the metabolism and excretion of [14C]-sunitinib (SU11248) in healthy male subjects. In: *Annual Meeting of the American Association for Cancer Research*. Los Angeles, California, USA: AACR; 2007. Abstract 9072.
13 Avastin prescribing information booklet. Genentech Inc. Rev February 2011; page 17 of 25.
14 Temsirolimus prescribing information booklet. Wyeth Pharmaceuticals Inc. Rev September 2010; page 17 of 22.
15 Launay-Vacher V, Oudard S, Janus N, Gligorov J, Pourrat X, Rixe O, *et al.* Prevalence of renal insufficiency in cancer patients and implications for anticancer drug management: the renal insufficiency and anticancer medications (IRMA) study. *Cancer* 2007; **110**:1376–1384.
16 Flanigan RC, Salmon SE, Blumenstein BA, Bearman SI, Roy V, McGrath PC, *et al.* Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med* 2001; **345**:1655–1659.
17 Maisonneuve P, Agodoa L, Gellert R, Stewart JH, Buccianti G, Lowenfels AB, *et al.* Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. *Lancet* 1999; **354**:93–99.
18 Lainakis G, Bamias A, Psimenou E, Fountzilas G, Dimopoulos MA. Sunitinib treatment in patients with severe renal function impairment: a report of four cases by the hellenic cooperative oncology group. *Clin Nephrol* 2009; **72**:73–78.
19 Rey PM, Villavicencio H. Sorafenib: tolerance in patients on chronic hemodialysis: a single-center experience. *Oncology* 2008; **74**:245–246.
20 Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, *et al.* Expressing the modification of diet in renal disease study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem* 2007; **53**:766–772.
21 Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, *et al.* Definition and classification of chronic kidney disease: a position statement from kidney disease: improving global outcomes (KDIGO). *Kidney Int* 2005; **67**:2089–2100.
22 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, *et al.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**:205–216.
23 Lee E, Wang JW. *Statistical methods for survival data analysis*. 3rd ed. Hoboken, New Jersey: Wiley & Sons Inc; 2003. pp. 76–91.
24 Khosravan R, Toh M, Garrett M, La Fargue J, Ni G, Marbury TC, *et al.* Pharmacokinetics and safety of sunitinib malate in subjects with impaired renal function. *J Clin Pharmacol* 2010; **50**:472–481.
25 Josephs D, Hutson TE, Pickering LM, Larkin JM, Choueiri TK, Patel TV, *et al.* Efficacy and toxicity of sunitinib in patients with metastatic renal cell carcinoma (mRCC) with severe renal impairment or on haemodialysis. In: 2009 ASCO Annual Meeting. Orlando, FL; 2009. p. J Clin Oncol 27:15 s (Supplement; abstr 5109).
26 Hutson TE, Figlin RA, Kuhn JG, Motzer RJ. Targeted therapies for metastatic renal cell carcinoma: an overview of toxicity and dosing strategies. *Oncologist* 2008; **13**:1084–1096.
27 Inauen R, Cathomas R, Boehm T, Koeberle D, Pestalozzi BC, Gillessen S, *et al.* Feasibility of using cetuximab and bevacizumab in a patient with colorectal cancer and terminal renal failure. *Oncology* 2007; **72**:209–210.
28 Garnier-Viougeat N, Rixe O, Paintaud G, Ternant D, Degenne D, Mouawad R, *et al.* Pharmacokinetics of bevacizumab in haemodialysis. *Nephrol Dial Transplant* 2007; **22**:975.
29 Gullestad L, Iversen M, Mortensen SA, Eiskjaer H, Riise GC, Mared L, *et al.* Everolimus with reduced calcineurin inhibitor in thoracic transplant recipients with renal dysfunction: a multicenter, randomized trial. *Transplantation* 2010; **89**:864–872.
30 Moro J, Almenar L, Martinez-Dolz L, Aguero J, Rueda J, Arnau MA, *et al.* mTOR inhibitors: do they help preserve renal function? *Transplant Proc* 2007; **39**:2135–2137.