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REVIEW

Sunitinib: the First to Arrive at First-Line Metastatic Renal Cell Carcinoma

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ABSTRACT

Tyrosine kinase inhibitors (TKIs) are beneficial for the treatment of renal cell carcinoma (RCC), gastrointestinal stromal tumors (GIST), pancreatic neuroendocrine tumors (pNETs), and other tumors. The antitumor activity of sunitinib has been based on time-related parameters such as progression-free survival (PFS) and overall survival (OS). Advances in knowledge of the molecular mechanisms and oncogenic processes associated with RCC have enabled the availability of rational targets for pharmacotherapy. Although each small molecule is modeled to block the activity of selected kinase signaling enzymes, it is increasingly evident that many have nontargeted effects (on other kinases) that may cause unexpected complications. The recommended dose for sunitinib in patients with advanced RCC is a 50 mg oral daily dose, with or without food, on a 4/2 week schedule (4 weeks "on" vs. 2 weeks "off") until progression. An alternative continuous 37.5 mg/day dosing schedule has also been evaluated and appears to be well tolerated, allowing the maintenance of the dose density of sunitinib with a similar outcome. The continuous administration schedule provides a constant exposure to the drug, and may prevent potential tumor regrowth and angiogenesis recovery. Most side effects are reversible and should not result in sunitinib discontinuation.

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In this article, the body of evidence behind the use of sunitinib in metastatic RCC (mRCC) compared to other targeted agents that have recently come into the field is summarized, and the need for correct management of an adverse event profile in order to better optimize available treatment options is underlined.

Keywords: Renal cell carcinoma; Sunitinib; Tyrosine kinase inhibitors

INTRODUCTION

Renal cell carcinoma is the most common cancer of the kidney. Up to 30% of patients with renal cell carcinoma present with metastatic disease, and recurrence occurs in nearly 40% of patients treated for a localized tumor [1]. New drugs are now well established for the treatment of patients with metastatic renal cell carcinoma. The use of these agents has improved overall survival to more than 2 years with sunitinib [2].

Sunitinib is a multitargeted oral tyrosine kinase inhibitor. It targets vascular endothelial growth factor receptor (VEGFR) 2, platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGF), FMS-like tyrosine kinase 3 (FLT-3), and stem cell factor receptor (c-KIT). VEGFR and PDFGR play a key role in the pathogenesis of clear cell carcinoma through involvement of the von Hippel-Lindau (VHL) gene, which is inactivated in up to 80% of sporadic cases of clear cell carcinoma. The protein encoded by VHL participates in the regulation of VEGF and PDGF, and so its inactivation causes overexpression of these agonists of VEGFR and PDGFR. The resulting persistent stimulation may promote tumor angiogenesis, tumor growth, and metastasis [3].

Sunitinib is approved by the US Federal Drug Administration (FDA) for the treatment of patients with advanced renal cell carcinoma at favorable or intermediate risk and in patients with imatinib-resistant gastrointestinal stromal tumors.

METHODS

In this review an extensive summary of the molecular basis of action, pharmacodynamic and pharmacokinetic properties, safety profile, efficacy, and biomarkers of sunitinib activity in first-line treatment of metastatic renal cell carcinoma is given.

A literature search was performed using sunitinib and metastatic renal cell carcinoma as keywords, and the most relevant prospective and retrospective studies and reviews published between 2003 and 2011 in different medical journals were selected. Studies published only as abstracts were excluded to give more scientific consistency to the review.

A brief review of the pivotal studies of the other targeted therapies approved for the same indication, such as bevacizumab, pazopanib, and tensirolimus, is also supplied so that they can be contrasted with the published data on sunitinib.

MOLECULAR BASIS OF ACTIVITY, PHARMACODYNAMICS, AND PHARMACOKINETICS PROPERTIES OF SUNITINIB

Modern oncology can be seen to rely on the discovery of biologically relevant targets and signaling pathways that are crucial for cancer survival. “Multitargeted” agents (eg, sunitinib, imatinib, or sorafenib) are known to block several receptors and intracellular kinases allowing them to achieve a broader spectrum of activity than single target inhibitors and conventional cytotoxic chemotherapy in the metastatic renal cell carcinoma (mRCC) field.

Sunitinib malate is a multitargeted tyrosine kinase inhibitor that competes with adenosine

Table 1. Pharmacokinetic parameters of sunitinib

F	Protein binding	t_{max} (hours)	$t_{1/2}$ (hours)	AUC_{0-24} (μg hour/mL)	$V_{d/F}$ (I)	$C_{L/F}$ (I/hour)	C_{trough} (ng/mL)
Unknown	95%	6-12	40-60	1.11	2230	34-62	44

AUC=area under the curve; $C_{L/F}$=apparent oral clearance; C_{trough}=trough concentration; F=absolute bioavailability; $V_{d/F}$=apparent volume of distribution.

triphosphate (ATP) for binding to the intracellular domain of class III and V receptors [4]. It inhibits vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, and VEGFR-3), platelet-derived growth factor receptors (PDGFR-alfa and PDGFR-beta), c-KIT, FLT-3, colony stimulating factor 1 receptor (CSF-1R), and glial cell line derived neurotropic factor receptor (rearranged during transfection [RET]) [4-7]. Sunitinib ultimately causes tumor growth delay and/or regression by inducing tumor cell death, inhibiting new blood vessel formation, and disrupting existing tumor blood vessels leading to central tumor cell necrosis and cavitation [4]. Sunitinib displays a preferential antiangiogenic effect but also possesses antitumor activity through its action not only on tumor cells but also on endothelial and pericyte cells.

High frequency ultrasound Doppler echography performed in patients receiving sunitinib reveals that intratumor vessels progressively disappear after 1 week of treatment, with an increase of necrosis in the central areas [4]. Although tumor regrowth during the 2-week "off" interval has been documented in some cases (both in vitro and in vivo), this is not usually clinically significant.

Pharmacodynamic studies in tumor-bearing mice predicted that sunitinib plasma levels greater than 50 ng/mL for at least 12 hours in a 24-hour dosing interval would inhibit target receptors sufficiently to achieve biological activity [4]. Pharmacokinetic parameters are summarized in Table 1. Pharmacokinetic investigations conducted in healthy volunteers and cancer patients have shown that following a single oral dose administration, sunitinib is rapidly absorbed and maximum plasma concentrations (C_{max}) occur between 6 and 12 hours (t_{max}) post dose [4]. In addition, sunitinib and its active metabolite SU12662 have been shown to display linear pharmacokinetics and have prolonged half-lives [4].

There is a large interpatient variability in exposure to sunitinib [5]. Bioavailability is not affected by food intake, and no significant changes in pharmacokinetic parameters are observed with repeated versus single dosing [4]. No differences in pharmacokinetics have been observed between healthy volunteers and cancer patients in individual studies.

Sunitinib is predominantly metabolized by cytochrome P450 3A4 (CYP3A4) in the liver to produce SU12662 and elimination occurs primarily via the feces (61%), with renal elimination accounting for only 16% of the administrated dose [4]. The terminal half-life was estimated to be 69 hours (interindividual variability 9%), and the absorption half-life 3.5 hours (interindividual variability 80%). Unlike other tyrosine kinase inhibitors, sunitinib does not appear to rely on active transport to enter into the cell, and it does not seem to be a high affinity substrate for most ATP binding cassette (ABC) efflux transporters. The study by Shukla et al. provided the first in vitro evidence of an interaction between sunitinib and the two major ABC drug transporters, *P*-glycoprotein and ATP binding cassette subfamily G member 2 (ABCG 2) [4]. This data may provide evidence for the observed interpatient variability in exposure after sunitinib oral uptake.

Mild or moderate hepatic impairment in patients did not significantly alter sunitinib

metabolism or total drug (TD) systemic exposure, and does not indicate a need to adjust the currently approved starting dose of sunitinib (50 mg on a 4/2 week schedule; 4 weeks "on" drug vs. 2 weeks "off") [8]. However, toxicity of 50 mg daily on the 4/2 week schedule may be more pronounced in patients with underlying liver dysfunction such as hepatitis B or C, fibrosis, and cirrhosis [4-6,8]. Severe renal impairment (creatinine clearance <30 mL/min) has no effect on the pharmacokinetics of sunitinib. Food has no effect on the bioavailability of the compound, and both area under the plasma concentration time curve and maximum plasma concentration increase dose proportionately with sunitinib 25-100 mg [5].

The dosing schedule of sunitinib 50 mg/ day for 4 weeks, with 2 weeks off, is based on the results of a pivotal phase 3 study. In a pharmacokinetic/ pharmacodynamic meta-analysis, Houk et al. found an association between sunitinib dose with longer time to tumor progression (TTP), longer overall survival (OS), a higher probability of a response, and greater decrease in tumor size. There was a relationship between dose and adverse effects, although these were mild or moderate [9]. Population pharmacokinetic analyses indicate that demographic data (age, body weight, race, gender, or Eastern Cooperative Oncology Group [ECOG] score) significantly modify exposure to sunitinib, but these variations were clinically irrelevant to explain pharmacokinetic differences between patients [4].

SUMMARY OF SUNITINIB CLINICAL ACTIVITY IN CLEAR CELL RENAL CELL CARCINOMA COMPARED TO OTHER TARGETED AGENTS

Luckily, the clear cell renal cell carcinoma (ccRCC) therapy armamentarium has become crowded in the recent years. The deeper knowledge of the molecular mechanisms involved in RCC pathogenesis and the relationship with VHL pathway alterations has led to the development of several antiangiogenic drugs in this field.

Different agents against tumor neovascularization are available to target ccRCC. In this sense monoclonal antibodies like bevacizumab can be used against soluble vascular endothelial growth factor (VEGF), drugs like temsirolimus or everolimus against the mammalian target of rapamycin (mTOR) or we may also target the receptors of proangiogenic factors such as VEGFR and PDGFR that are involved in new blood vessel formation [8]. Sunitinib, sorafenib, and pazopanib are multitargeted agents directed against the ATP binding site on the intracellular domain of VEGF and PDGF membrane receptors. Although these multitargeted agents seem to have the same mechanism of action, the profile of kinase inhibition induced by either single agent alone is very different [4]. This uniqueness is thought to be directly related to both clinical activity and toxicity profile.

The recent approvals of several targeted agents with somewhat overlapping indications for ccRCC treatment may complicate therapeutic decisions, and the large amount of data recently communicated in this field can lead to confusion.

Sunitinib and sorafenib were the first two biological drugs approved by health authorities for the treatment of patients with advanced RCC. Three out of four patients with advanced ccRCC who were treated with sunitinib, from a total of 28 patients recruited for a phase 1 trial, achieved durable partial response on the Response Evaluation Criteria in Solid Tumors (RECIST) scale (28, 36, and 54 weeks lasting response). This fact, together with the biological rationale, led to two consecutive phase 2 noncomparative trials in 63 and 106 cytokine-refractory

metastatic RCC patients. The radiological response rate achieved was 40% and 44%, and the median progression-free survival (PFS) was 8.7 and 8.3 months, respectively [4,5]. Based on the clinical activity, never seen before with this tumor, sunitinib was compared in an international, multicenter, randomized phase 3 trial with interferon-alfa in a first-line treatment setting for metastatic RCC patients [10]. A total of 750 patients were included in the study. Sunitinib clearly showed superiority versus interferon-alfa for the primary endpoint of the study, which was PFS (11 vs. 5 months; HR=0.42 [95% CI, 0.32 to 0.54]). Treatment with sunitinib was also associated with a higher response rate of 31% (95% CI, 26% to 36%) compared with the interferon-alfa group (95% CI, 4% to 9%; $P<0.001$) by independent radiologic review. Overall survival (OS) was 26.4 months for sunitinib versus 21.8 months for interferon; $P=0.051$. OS subanalysis that excluded the impact of subsequent treatments showed that patients treated with sunitinib achieved an OS of 28.1 months versus 14.1 months in the interferon arm ($P=0.0033$) Based on these results, sunitinib became the new standard for first-line treatment in mRCC.

Sunitinib clinical evidence was also shown beyond the phase 3 clinical trial in an expanded access program that included 4,564 patients with mRCC, representing a real world setting. In this study sunitinib achieved comparable benefits to the phase 3 trial, with a median PFS of 10.9 months (95% CI, 10.3 to 11.2) and a comparable side effects profile. But most importantly, sunitinib also showed a clear benefit in other populations such as older patients, with a PFS of 11.3 months, those with nonclear cell histology (PFS 7.8 months), patients with an ECOG score >2 (PFS 5.1 months) and subjects with brain metastasis (PFS 5.6 months) [11].

As well as the pivotal data on sunitinib, randomized data for other agents in first-line RCC is also available.

Two randomized trials were reported for bevacizumab plus interferon-alfa, the multinational avastin and roferon in renal cell carcinoma (AVOREN) trial and the American cancer and leukemia group B (CALGB) 90206 study, which had almost identical designs. These trials compared the combination of bevacizumab plus interferon-alfa versus interferon-alfa alone. No differences for the main endpoint of the study (OS) were detected either in AVOREN (22.9 vs. 20.6 months $P=0.1291$) nor in the CALGB trial (18.3 vs. 17.4 months $P=0.069$). Nevertheless, PFS was longer for those patients treated with the combination arm both in AVOREN (10.2 vs. 5.5 months; HR=0.63) and CALGB trial (8.4 vs. 4.9 months; HR=0.71) [12-14].

Sternberg et al. reported on a phase 3 trial (VEG105192) that compared pazopanib versus placebo instead of interferon-alfa. A total of 435 patients with advanced RCC were included in the study both as patients receiving first-line treatment and also patients who had received a previous cytokine regimen. PFS, the main endpoint of the study, was prolonged in patients who received pazopanib compared with those who received placebo (9.2 vs. 4.2 months; HR=0.46; $P<0.001$). However, no differences were demonstrated in overall survival: 22.9 months for pazopanib versus 20.5 months for placebo (HR=0.91 stratified log rank P value: 0.224) [15].

The Global Advanced Renal Cell Carcinoma (ARCC) trial is a phase 3 trial that compared temsirolimus as a single agent with interferon-alfa alone or the combination of temsirolimus plus interferon-alfa. Patients included in the study were those with poor risk prognostic according to modified Memorial Sloan-Kettering Cancer Center (MSKCC) criteria. Temsirolimus given as

Table 2. Clinical efficacy data from randomized trials with targeted agents in first-line treatment of metastatic renal cell carcinoma (RCC) patients.

Lead author/ reference	Treatment	*n*	Patient characteristics	ORR (%)	PFS (months)	OS (months)
Motzer [10]	Sunitinib	750	First line (good and intermediate prognosis)	47	11	26.4
	Interferon-alfa			12	5	21.8
	Interferon-alfa			9	5.6	NR
Escudier [17]	Bevacizumab + interferon-alfa	649	First line (good and intermediate prognosis)	31	10.4	22.9
	Interferon-alfa			12	8.4	20.6
Rini [13]	Bevacizumab + interferon-alfa	732	First line (good and intermediate prognosis)	26	8.4	18.3
	Interferon-alfa			13	4.9	17.4
Sternberg [15]	Pazopanib	435	First line and second line (after cytokines)	30	9.2	22.9
	Placebo			3	4.2	20.5
Hudes [16]	Interferon-alfa	626	First line (poor prognosis by modified MSKCC criteria)	5	3.1	7.3
	Temsirolimus			9	5.5	10.9
	Temsirolimus + interferon-alfa			8	4.7	8.4

MSKCC=Memorial Sloan-Kettering Cancer Center; NR=not reported; ORR=overall response rate by investigator assessment; OS=overall survival; PFS=progression-free survival.

Table 3. Clinical efficacy data for targeted agents approved and in development for the treatment of metastatic renal cell carcinoma in Europe/USA.

Agent	Median PFS (months)	*P* value	Median OS (months)	*P* value	Reference
Sunitinib	11	<0.001	26.4	0.051	[10]
Temsirolimus	5.5	0.0001	10.9	0.0069	[16]
Sorafenib	5.5	<0.001	17.8	0.146	[17]
Everolimus (overall)	4.9	<0.001	14.8	0.177	[18]
Pazopanib (overall)	9.2	<0.0001	22.9	0.52	[15]

OS=overall survival; PFS=progression-free survival.

a single agent showed a statistically significant better OS than interferon-alfa, 10.9 versus 7.3 months respectively (HR=0.73, *P*=0.008) [16].

Activity data from randomized trials conducted in the first-line setting of metastatic RCC patients are summarized in Tables 2 and 3 [10,13,15-18]. There are no direct comparisons between the different drugs available for first-line treatment. Ongoing trials, such as the "Pazopanib Versus Sunitinib in the Treatment of Locally Advanced and/or Metastatic Renal Cell Carcinoma" (COMPARZ trial), that evaluates the efficacy and safety of pazopanib compared to sunitinib as first-line treatment in patients with advanced or metastatic RCC, will assess if pazopanib is noninferior to sunitinib [19].

DOSAGE AND ADMINISTRATION

The study design, population, and timing of measurements varied between studies [2,10,20]. Sunitinib doses in the earlier trials ranged from 25-150 mg administered once every day or every other day. Phase 1 trials determined that the maximum tolerable dose of sunitinib is 50 mg per day. For better tolerance and adherence a 4 weeks "on" and 2 weeks "off" scheme was developed. In clinical practice dose modifications in 12.5 mg steps are allowed. Achieving optimal exposure to sunitinib appears to be important for maximizing clinical benefit.

Following a single oral dose, peak plasma sunitinib concentrations are reached after 6-12 hours. Sunitinib and its primary metabolite, SU12662, have demonstrated linear pharmacokinetics and have long half-lives (40 and 80 hours, respectively), supporting a once daily dosing regimen [8]. Studies of sunitinib have demonstrated that covariates such as gender, age, and ECOG score affected sunitinib clearance, but these effects only account for a small proportion of the estimated interindividual variability in apparent clearance (CL/F) and hence were not considered clinically relevant [21].

An alternative continuous dosing 37.5 mg/day sunitinib schedule has also been evaluated in renal and neuroendocrine carcinomas. Theoretically the continuous administration schedule provides a constant exposure to the drug, and may thus prevent potential tumor regrowth and angiogenesis recovery during off treatment periods. With the hypothesis that continuous treatment could have equal or greater efficacy with better tolerability, the randomized phase 2 multicenter study of the efficacy and safety of sunitinib on the 4/2 versus continuous dosing schedule as first-line therapy of metastatic RCC (Renal EFFECT trial) in patients with cytokine-refractory mRCC was developed. Unfortunately in this trial there was a trend toward inferior TTP with continuous dosing; overall response rate (ORR), OS, and adverse event (AE) profiles were similar for the approved sunitinib 50 mg/day dose on the 4/2 week schedule versus 37.5 mg continuous dosing [22].

Patients with a higher exposure to sunitinib are associated with improved clinical outcomes (eg, longer TTP, longer OS, and a trend toward a higher probability of tumor size reduction or halting of tumor growth), as well as some increased risk of AEs [9,23]. Patients with the highest exposure to sunitinib displayed longer TTP and OS. This relationship was consistent across the different tumor types assessed. Similar results were seen when the data was analyzed using total drug concentrations.

Increased exposure was associated with AEs; however, these were generally mild to moderate in severity. It has been suggested that certain AEs could have a greater impact in specific patient subgroups such as older patients and/or patients with comorbidities, and that these patients may require further support. Results from the expanded access

program demonstrated that sunitinib can be administered long-term (>6 months) without any cumulative toxicity [11].

Adequate drug exposure is required to optimize the antitumor effect of sunitinib. Pharmacokinetic analyses have demonstrated that sunitinib plasma concentrations correlate significantly with the probability of a partial response and TTP in cytokine-refractory patients. Since increased exposure to sunitinib is associated with improved clinical efficacy, the therapeutic goal should be to administer sunitinib at the highest tolerated dose for each patient, and to minimize dose delays, reductions, or discontinuation secondary to treatment related AEs [9].

Regarding treatment duration, it is important to note that in the phase 3 trial, response rates increased with longer sunitinib durations. This finding suggests that in clinical practice, the goal should be to keep patients on therapy while clinical benefit is observed. Maximizing the clinical outcome of sunitinib therapy requires anticipation of AEs and early intervention to avoid treatment delays and dose-limiting toxicities [24].

TOLERABILITY

Owing to the inherent selectivity of targeted drugs, these agents are generally associated with lower toxicity compared to conventional systemic cytotoxic drugs. Most of the safety data published comes from large phase 3 trials using the recommended sunitinib dose of 50 mg/day for 4 weeks every 6 weeks, and this shows mild to moderate, manageable, and reversible toxicities [2,10,16-17] (Tables 4-7).

Toxicity Profile

Phase 1 Repeat Dosing Studies

Sunitinib was studied using various schedules (2/1, 2/2, or 4/2). Early sunitinib phase 1 included single dose studies of oral drug in healthy adults to assess toxicity and pharmacokinetic parameters [5]. Dose-limiting toxicities of fatigue, asthenia, and thrombocytopenia occurred at 75 mg in all schedules, thereby establishing the recommended dose in phase 2 studies of 50 mg with 2/1, 2/2, or 4/2 week schedules.

Fatigue was the most commonly reported adverse event for patients enrolled in phase 1 studies. This symptom was associated with lethargy. Asthenia, weakness, and malaise were often dose limiting. Fatigue seemed to be dose dependent, it was less frequent with the 25 mg/day dose and more frequent with the 75 mg/day dose at which it was also more frequently of grades 3/4 severity [24].

Phase 2 Clinical Trials

Toxicities in these studies were similar to those reported in the phase 1 studies. Fatigue was the most common event with grade 3 toxicity.

Table 4. Global toxicity of tyrosine kinase inhibitors.

Drug	Target	Description	Toxicity
Sunitinib	VEGFR, PDGFR, c-KIT, FLT-3	Small multikinase inhibitory molecule	Asthenia, diarrhea, hypertension, hypothyroidism, hand-foot syndrome, dermatologic adverse reactions, mucositis
Sorafenib	VEGFR2, VEGFR3, PDGFR, c-KIT, FLT-3, RET, RAF1	Small multikinase inhibitory molecule	Asthenia, diarrhea, rash, hand-foot syndrome, hypertension

c-KIT=stem cell factor receptor; FLT-3=FMS-like tyrosine kinase 3; PDGFR=platelet-derived growth factor receptors; RET=rearranged during transfection; VEGFR=vascular endothelial growth factor receptors.

Phase 3 Clinical Trials

The phase 3 trial of oral sunitinib in first-line therapy enrolled patients with good and intermediate risk ccRCC. Adverse events observed commonly in patients treated with sunitinib were constitutional (fatigue), gastrointestinal (diarrhea, nauseas, mucositis, stomatitis, and vomiting), hypertension (HTN), hand-foot syndrome, and laboratory and hematologic abnormalities. The most common sunitinib adverse events were diarrhea, fatigue nausea, stomatitis, vomiting, and hypertension [10]. Both hematology and chemistry laboratory test abnormalities were also reported.

It has been observed that proteinuria induced by sunitinib was significantly greater in those patients who experienced HTN, a class adverse event effect of antiangiogenic agents [25]. The presence of HTN varied between 15% and 28% in prospective clinical trials with sunitinib. However, severe grade 3 or greater HTN was only reported in the range of 8% to 10% [2,26].

Drug related HTN can occur with drug initiation (during the second cycle) and within the first year of treatment. In general tyrosine kinase inhibitor (TKI)-associated HTN is an emerging toxicity that is developed by patients treated with TKIs compared with patients treated with placebo [2].

TKI-induced hand-foot skin reactions (HFSR) of any grade (considered as a subclass of palmar erythrodysesthesia, which is more localized) were observed in 9% to 42% of patients treated with sunitinib, whereas skin reactions grade 3 or 4 were observed in 4% to 16% of patients [2,10].

Sunitinib-induced skin rash of any grade occurred in 3% to 19% of patients whereas skin rash of grade 3 or 4 was seen in 0% to 2% of patients. The development of skin xerosis was seen in 16% of patients. Dermatitis of any grade was reported in 8% of patients whereas 2% of all patients developed dermatitis of grade 3 or 4 [2]. Skin toxicity typically occurred after therapy with TKIs, with reversible symmetric palm and sole acral erythema [27,28]. A distinct degree of hair depigmentation (gray coloration of scalp or facial hair) occurred in about 60% of patients treated and was visible after the first two cycles of treatment. The overall incidence of hair color changes in patients treated with sunitinib is approximately 7%, whereas depigmentation of the skin reached 16% to 28% [2,11,29].

Sunitinib-related cardiac toxicities included left ventricular dysfunction, arrhythmias, and PR and QT prolongation. Left ventricular dysfunction, which manifested as a decrease in left ventricular ejection fraction (LVEF), has been reported in up to 12% of patients, but symptomatic ventricular dysfunction was only seen in 1% to 2% of patients [2].

The electrocardiogram alterations include changes in rhythm, conduction disturbances, changes in axis and QRS amplitude, ST segment depression and elevation, alteration in T and QT prolongation. The abnormalities observed in echocardiograms were related to LVEF, regional contractile dysfunctions, relaxation disturbances, and pericardial effusion. Another noncardiac vascular event was the acute occlusion of arteries [2,11]. In phase 2 clinical trials, cardiotoxicity induced by sunitinib was observed in 4.7% of patients who underwent a decrease in LVEF in echocardiogram [10].

Hypothyroidism has been reported in nearly 80% of patients receiving sunitinib [30-32]. Thyroid abnormalities were detected relatively early from the beginning of the treatment. Moreover, the incidence of hypothyroidism seems to increase progressively with the duration of sunitinib therapy. Analysis of thyroid-stimulating hormone (TSH) serial measurements during a clinical trial of sunitinib showed abnormal TSH concentrations in serum in 65% patients, and 53% developed persistent

Table 5. Grade ≥3 adverse events with sunitinib 50 mg, oral, daily ×4 weeks, 2 weeks off, reported in treated patients in phase 3 trials in renal cell carcinoma [10].

Type	All grades (%)	Grades 3-4 (%)
Systemic		
Fatigue/asthenia	58	7
Hypothyroidism	71	?
Cardiovascular		
Hypertension	24	8
Declined LVEF	10	
Respiratory		
Dyspnea	16	1
Gastrointestinal		
Diarrhea	53	5
Mucositis/stomatitis	45	3
Nausea	44	3
Vomiting	24	4
Dyspepsia	28	1
Anorexia	28	1
Dysgeusia	44	1
Abdominal pain	22	3
Dermatologic		
Hand-foot syndrome	20	5
Rash	19	12
Skin discoloration	16	?
Edema	11	1
Laboratory abnormalities (hematology)		
Neutropenia	72	12
Lymphopenia	60	12
Thrombocytopenia	65	8
Anemia	71	4
Laboratory abnormalities (biochemistry)		
↑ Creatinine	66	1
↑ Lipase	52	16
↑ Uric acid	41	?
↓ Phosphorous	36	5
↑ Glucose	18	4

LVEF=left ventricular ejection fraction; ?=unknown/not given.
Graded according to the NCI Common Terminology Criteria for Adverse Events, version 3.0.

primary hypothyroidism for a long period. In all reported series, intermittent hypothyroidism was demonstrated. TSH concentrations in serum increased at the end of the "on" phase in the treatment cycle and were near normal at the end of the "off" phase. It is also known that after 5 months, sunitinib causes hypothyroidism in 53% of patients, and on average, hypothyroidism appears after 54 weeks. The probability of hypothyroidism increases with time and each cycle of treatment [33]. After several treatment cycles, baseline TSH levels seem to increase, revealing a permanent hypothyroidism. Although abnormalities in thyroid function commonly arise during treatment with sunitinib, hypothyroidism was clinically detected only rarely in large studies [2].

The more clinically relevant gastrointestinal adverse effects related to TKIs are: diarrhea (20% of patients), anorexia, and functional mucositis, followed by mouth pain, difficulty in swallowing, nausea, vomiting, and dysgeusia [2,24]. The emetogenic toxicity of sunitinib is low, but nausea seems to occur frequently. Other gastrointestinal adverse effects such as dry mouth and oral changes, stomatitis, heartburn, dysgeusia, flatulence, bloating, and constipation occur with variable frequency [10,24].

Patients on sunitinib therapy had high rates of hematologic toxicities (Table 5) [10]. The safety and toxicity of sunitinib were assessed in a phase 1 trial, when hematologic toxicities mostly consisted of thrombocytopenia and neutropenia [24]. In the initial phase 3 trial, all grade anemia, leucopenia, neutropenia, and thrombocytopenia occurred in 60% to 70% of patients treated with sunitinib [10]. Phase 3 data indicate that of all mRCC patients receiving sunitinib malate, 11%, 5%, and 6% show grade 3 neutropenia, leucopenia, and thrombocytopenia, respectively [2]. Important grade 4 laboratory adverse events consisted of

Table 6. Percentage of patients affected by toxicities associated with tyrosine kinase inhibitor administration.

	Sunitinib [10]	Temsirolimus [16]	Sorafenib [17]	Placebo
General symptoms				
All grades:				
Asthenia	68	51	37	28
Flu-like syndrome	19	32	24	-
Anorexia	-	32	16	13
Depression	-	-	-	-
Grades 3-4:				
Asthenia	11	11	5	4
Flu-like syndrome	3	2	-	-
Anorexia	-	3	-	1
Depression	3	-	-	-
Cardiovascular toxicity				
All grades:				
Hypertension	24	-	17	2
Cardiac toxicity	10	-	-	-
Dyspnea	-	28	14	12
Grades 3-4:				
Hypertension	8	-	4	<1
Cardiac toxicity	2	-	-	-
Dyspnea	-	9	4	2
Skin toxicity				
All grades:				
Hand-foot syndrome	21	0	30	7
Rash	19	47	40	16
Alopecia	-	-	27	3
Discoloration	16	-	-	-
Pruritus	-	-	19	6
Grades 3-4:				
Hand-foot syndrome	5	0	6	0
Rash	2	4	<1	<1
Alopecia	-	-	<1	0
Discoloration	0	-	-	-
Pruritus	-	-	<1	0
Digestive symptoms				
All grades:				
Emesis	44	56	39	31
Diarrhea	53	27	43	13
Mucositis	25	20	-	-
Grades 3-4:				
Emesis	7	4	2	2
Diarrhea	5	1	2	1
Mucositis	1	1	-	-

Table 7. Percentage of patients affected by toxicities associated with tyrosine kinase inhibitor administration.

	Sunitinib [10]	Temsirolimus [16]	Sorafenib [17]
Hematologic toxicity			
All grades:			
Leucopenia	78	6	-
Neutropenia	72	7	-
Anemia	71	45	8
Thrombocytopenia	65	14	-
Lymphopenia	60	-	-
Grades 3-4:			
Leucopenia	5	1	-
Neutropenia	12	3	-
Anemia	4	20	3
Thrombocytopenia	8	1	-
Lymphopenia	12	-	-
Analytical alterations			
All grades:			
↑ GOT	46	8	-
↑ GPT	52	-	-
↑ Bilirubin	19	-	-
↑ Alkaline phosphatase	42	-	-
↑ Creatinine	66	10	-
↑ Amylase	32	-	-
↑ Lipase	52	-	-
↑ Uric acid	41	-	-
↑ Phosphatemia	36	-	-
↑ Lipids	-	51	-
↑ Glucose	-	26	-
Grades 3-4:			
↑ GOT	2	-	-
↑ GPT	3	1	-
↑ Bilirubin	1	-	-
↑ Alkaline phosphatase	2	-	-
↑ Creatinine	1	3	-
↑ Amylase	5	-	-
↑ Lipase	16	-	-
↑ Uric acid	12	-	-
↑ Phosphatemia	5	-	-
↑ Lipids	-	4	-
↑ Glucose	-	11	-

GOT=glutamic-oxaloacetic transaminase; GPT=glutamic-pyruvic transaminase.

1% anemia and 1% neutropenia; blood counts usually recover during the 2 weeks off drug period. Although the onset of hematologic toxicity can occur in the first cycle of treatment, it is usually detected on day 28 and it is rare to see progressive hematologic toxicity with an increasing number of cycles, although recurrences of low blood counts are common.

Laboratory abnormalities have also been described. Among patients treated with sunitinib, creatine kinase MB was found increased in 23% of cases. In 10% of cases this increase was associated with clinical symptoms. Sunitinib also induces an elevation of amylase and lipase without pancreatic failure or inflammation [2,10].

The occurrence of other infrequent toxicities have also been observed in patients treated with sunitinib: fever in 13% (grades 1 and 2), myalgia in 11% (grade 1 and 2), periorbital edema in 11% (grade 1), dizziness in 10% (grades 1 and 2), edema in 7% (grade 1 and 2), muscle weakness in 4% (grades 2 and 3), and cognitive disorders in 4% (grade 2 and 3) [2].

Toxicities as Biomarkers

The available evidence regarding sunitinib toxicities as biomarkers is limited and is based on retrospective series' with small number of patients.

HTN has been one of the most studied toxicities. Rini et al. published a retrospective analysis in patients with RCC cell carcinoma who were treated with sunitinib, and concluded that sunitinib-associated HTN is associated with improved clinical outcome measured in terms of OS, disease-free survival (DFS) and response rates (RR), without clinically significant increases in HTN-associated adverse events [34].

Other toxicities such as asthenia, fatigue, or hematologic toxicities (neutropenia, thrombocytopenia) have been evaluated in retrospective studies in order to evaluate their possible roles as biomarkers, but the results should be validated in prospective studies.

ROLE OF SUNITINIB IN METASTATIC RENAL CELL CARCINOMA

Management of mRCC has changed considerably since the introduction of multitarget TKIs and mTOR inhibitors. TKIs can lead to shrinkage of disease in a fraction of patients with mRCC, but most cases (50% to 70%) have disease control while on treatment. There is no solid data on the activity of sunitinib in nonclear cell histology. Moreover, OS data for chromophobe, collecting duct, and papillary RCC cases are worse than in clear cell tumors [35]. Even so, sunitinib data in terms of PFS are superior if compared to similarly designed trials conducted with sorafenib in patients with nonclear histologies (11.9 vs. 5.1 months) [36].

Sorafenib has demonstrated activity as a treatment for patients with clear cell mRCC who have cytokine-refractory disease [17]. There is no trial that shows benefit in the first-line setting over interferon-alfa treatment alone, but it has been demonstrated to provide clinical benefit in a second-line setting after cytokine treatment.

Pazopanib is another multitarget inhibitor with similar targets to sunitinib, including VEGFRs, PDGFRs alfa and beta, and c-KIT [15]. Axitinib is a new generation multitarget inhibitor that inhibits VEGFR, PDGFR-beta, and c-KIT with a higher affinity that sunitinib in the preclinical setting, and has demonstrated activity as second-line therapy in patients with mRCC [34]. Temsirolimus is an intravenous mTOR inhibitor approved for the treatment of poor risk RCC patients, including nonclear cell carcinoma [16]. Everolimus is another mTOR inhibitor found to have activity in RCC [18,37]. The recommended dose for everolimus is 10 mg/day,

as an oral dose, in second-line treatment after progression to a TKI.

CONCLUSION

Nowadays, targeted agents represent the backbone of systemic treatment for advanced and/or metastatic RCC, and have largely replaced cytokine therapy due to improvements in both efficacy and tolerability. Sunitinib is a standard treatment for good and intermediate risk clear cell mRCC. Phase 3 results indicated an unprecedented median OS of over 2 years in mRCC patients who received first-line treatment with sunitinib. This is the longest survival period ever reported in a randomized trial conducted in mRCC patients.

Other targeted agents licensed for mRCC that have also demonstrated efficacy for the treatment of this disease include sorafenib, bevacizumab given in combination with interferon-alfa, temsirolimus, and everolimus. In the near future there are a number of new targeted agents for mRCC being investigated, including pazopanib, axitinib, vandetanib, tivozanib, and linifanib among others.

Sunitinib is associated with a predictable and manageable tolerability profile; most AEs are mild or moderate in severity and can be managed with routine medical interventions.

In order to obtain optimal benefit from sunitinib, patients should start at the recommended starting dose of 50 mg/day on a 4/2 week schedule (4 weeks "on" vs. 2 weeks "off") and dose adjustment should be avoided by effective management of treatment-related AEs. In those patients for whom it may not be possible to maintain a full dose, it may also be useful the administration of alternative dosing schedules (eg, 4/2, 3/2, 2/2, or 2/1). The safety/tolerability profile of sunitinib administered continuously at 37.5 mg/day appears similar to that of sunitinib administered on a 4/2 week schedule.

The highest dose the physician is able to achieve and maintain will give the highest efficacy in terms of OS, TTP, and overall objective response rate. However, the highest dose achieved has also been correlated with the highest toxicity. The balance between efficacy and toxicity is a key factor in a patient's clinical outcome. Therefore, it is essential that physicians know how to treat sunitinib toxicities to avoid dose reductions or delays that compromise its effectiveness.

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