REVIEW ARTICLE

Novel Therapies in Advanced Renal Cell Carcinoma

Management of Adverse Events From Sorafenib and Sunitinib

Philipp Ivanyi, Thomas Winkler, Arnold Ganser, Christoph Reuter, Viktor Grünwald

SUMMARY

Introduction: Sorafenib and Sunitinib are the first tyrosine kinase inhibitors licensed for the treatment of advanced renal cell carcinoma. In contrast to conventional chemotherapy, targeted therapies have distinct and specific side effects.

Methods: Selective review in Medline and the data base of the American Society of Clinical Oncology on the treatment and side effects of tyrosine kinase inhibitors in renal cell carcinoma, drawing on the authors' own experience.

Results and discussion: Tyrosine kinase inhibitors are characterized by a variety of uncommon side effects, such as lassitude, mucosal inflammation and skin changes. The detection and treatment of adverse events are critical for interdisciplinary cancer treatment in order to ensure patients´ safety. This article offers an overview of the unwanted effects of drug therapy in the management of renal cell carcinoma.

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Key words: renal cell cancer, kinase inhibitor, sorafenib, sunitinib, molecular targeted therapy

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Renal cell carcinoma is a heterogenous tumor entity, with both classical histological characteristics and characteristic genetic changes, which have a major influence on the choice of treatment. The most frequent subtype of renal cell carcinoma (RCC) is clear cell RCC, characterized by a loss in function of the von Hippel-Lindau (VHL) protein (e1). This loss of function in the cell causes activation of cellular signal cascades, leading to formation of new tumor vessels in this densely vascularized tumor. This process is known as neoangiogenesis (1, 2, e1–e3). The relevance of these signaling pathways for physiological processes within the cell is unclear in many areas and does not allow any reliable conclusions about the development of potential adverse drug reactions.

The increased understanding of the characteristic changes during carcinogenesis has made it possible to develop substances which have a pharmacological effect on the malfunctioning signal network in clear cell RCC. In 2006, sunitinib and sorafenib were licensed, the first tyrosine kinase inhibitors (TKI) for the treatment of metastatic or advanced RCC (3, e4, e5). Large licensing studies have demonstrated the efficacy of both of these substances; meta-analyses have not yet been published (4, 5). It has been shown that sunitinib is superior to interferon, with respect to tumor response and progression-free survival; increased overall survival has not yet been demonstrated (4). This substance was licensed for treatment of advanced RCC. It has been shown that sorafenib is superior to placebo after failure of prior immunotherapy. Moreover, prolongation of overall survival has been shown in comparison to placebo (5). Sorafenib has been licensed for the treatment of RCC after failure of immunotherapy, or if this is contraindicated.

The spectrum of blocked signal molecules determines the tumor response, and presumably also the substance-specific adverse effects (6). Thus, class-specific adverse effects have been described for these therapies. These also differ for the different substances, depending on the degree of inhibition of the different signal molecules. The most frequent adverse drug reactions with sunitinib and sorafenib are arterial hypertension, fatigue, skin changes, and gastrointestinal toxicity (4, 5). In particular, the rarer adverse drug reactions cannot be adequately recorded in

licensing studies and must be critically observed in normal clinical practice. One such clinically relevant adverse drug reaction is hypothyroidism, which only becomes evident during routine use of these drugs and was not adequately recorded during the licensing study. The spontaneous recording system for drug adverse effects has been legally established in Germany since 1978 and includes adverse reactions which only occur in the course of clinical use, outside studies. This is a legal obligation for practicing doctors and makes a major contribution to drug safety within Germany.

As part of an expanded licensing program, the therapeutic safety of the TKIs was studied in ca. 7500 additional patients. Data from 3997 of a total of 5000 enrolled patients are available for evaluation of sunitinib. For sorafenib, data from all 2502 patients can be evaluated. Patients with advanced RCC could be included in these studies, including patients with CNS metastases and in poor general condition, who were excluded from prior studies. As both toxicity and efficacy were systematically recorded, the licensing study could be controlled on a much larger and less selected group of patients (7, 8). Both substances were administered orally, so that patients could be treated near their homes, without being constantly bound to a specialized center. Routine follow-up by the responsible specialists was normally performed every four to eight weeks. However, adverse drug reactions, such as arterial hypertension, often develop between the follow-up visits. Collaboration with the general practitioner is therefore absolutely essential, e.g., for optimal blood pressure control.

In this article, the authors indicate the typical adverse drug reactions from treatment of RCC with tyrosine kinase inhibitors, together with their characteristics and the possibilities for supportive treatment. These are of relevance for all doctors involved in treatment (e6). The literature search was based on data from the electronic database Medline and the bibliographic index of the annual meeting of the American Society of Clinical Oncology.

Adverse drug reactions

Severe adverse drug reactions which were grade 4 according to the "common toxicity criteria" (CTC) *(table 1)* occurred in fewer than 10% of patients being treated with sorafenib or sunitinib. Nevertheless, dose adjustment, a treatment-free interval or treatment discontinuation were necessary in a significant proportion of patients *(table 2)* (4, 5). *Tables 2 and 3* provide an overview of the spectrum of adverse effects, together with possibilities for supportive treatment. There are no data from controlled studies on supportive treatment, so that the authors' recommendation on monitoring and treatment are based on the opinion of experts.

Gastrointestinal toxicity

Diarrhea is one of the most frequent drug reactions with sorafenib and sunitinib, although this only reached CTC grade 3 or grade 4 in 2% of patients with sorafenib and in 5% of patients with sunitinib. With this degree of severity, therapy must be discontinued until the initial findings are re-established, or the symptoms subside to grade 1. The dose should be reduced in subsequent cycles *(table 4)* (4, 5).

Mucosal inflammation in the form of stomatitis and mucositis is a typical adverse drug reaction with sunitinib; this rapidly regresses during the two-week treatment-free interval (4). In the licensing study for sorafenib, this was only regarded as a minor adverse effect, even though 35% of patients suffered this drug reaction during phase II testing (5, 9). In contrast to mucosal toxicity associated with chemotherapy, the symptoms with molecular therapy are often purely functional, accompanied by taste disorders. Nevertheless, these adverse effects can impair quality of life in the long term, because of the protracted administration of these substances. It is recommended that the symptoms should be curbed and controlled at an early stage by changes in diet and intensive care of the mucous membranes. If the symptoms become more severe, pharmacological intervention is often necessary *(table 4)*. Aside from symptomatic treatment, a treatment-free interval

TABLE 1

Severity of adverse drug reactions according to the common toxicity criteria (CTC)

Severity	Clinical Severity of the Drug Reaction
0	None
1	Mild
2	Moderate
3	Severe
4	Life-threatening or disabling
5	Fatal

TABLE 2

Frequency of changes in the therapy with tyrosine kinase inhibitors in advanced renal cell carcinoma

	Sunitinib (%)	Sorafenib (%)
Administration scheme	50 mg day 1–28, then 2 weeks interval, p.o.	2 x 400 mg continuous, p.o.
Treatment-free interval	38	21
Dose reduction	32	13
Treatment discontinuation	8	10

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TABLE 3

Specific adverse drug reactions during treatment with tyrosine kinase inhibitors for renal cell carcinoma (severity grade according to CTC [5, 11])

Toxicity	Sunitinib (%)		Sorafenib (%)	
	All grades	Grades 3/4	All grades	Grades 3/4
Diarrhea	53	5	43	2
Lassitude	51	7	37	5
Nausea	44	3	23	< 1
Stomatitis	25	1	No data	No data
Vomiting	24	4	16	1
Hypertension	24	8	17	4
Hand-foot-skin reaction	20	5	30	6
Mucositis	20	2	No data	No data
Exanthema	19	2	40	1
Alopecia	No data	No data	27	< 1
Xeroderma	16	1	No data	No data
Nosebleed	12	1	No data	No data
Dry mouth	11	0	No data	No data
Hypothyroidism	34–84	No data	18	No data

CTC, common toxicity criteria

and dose adjustment are necessary if severe mucosal toxicity (grade 3 or 4) develops.

Constitutional symptoms

Treatment-associated fatigue, impairing daily life in the long term, has been described for 7% of patients with sunitinib and 5% of patients with sorafenib; this must be distinguished from secondary forms of exhaustion (4, 5, 6, 10–12). Appropriate controls should therefore be performed as part of normal oncological practice. The emetogenic potential of sunitinib and sorafenib is low (4, 5). Antiemetics, proton pump inhibitors, and drugs to protect the mucus membranes can be used to provide supportive therapy *(table 3, table 4, table 6)*.

Cutaneous toxicity

Exanthema or a hand-foot-skin reaction may develop during treatment with sorafenib or sunitinib *(table 3)* (4, 5). Patients who perform mechanically demanding activities are predisposed for this reaction, particularly at hyperkeratotic sites, where callus-like pustules with erythema and dysthesia may develop (6, 13, 14). Desquamation may occur with sunitinib, but at almost unpredictable times. The predominant symptom with sorafenib is painful hyperkeratosis, mostly occurring between the fourth and seventh weeks of therapy. *Table 4* lists local measures for the prevention and treatment of these symptoms. Specific adverse drug reactions under sunitinib include inhibition of hair pigmentation in 14% of all treated patients and temporary yellow coloration of the skin in 16% of patients (4, 10).

Arterial hypertension

Arterial hypertension is a class-specific adverse reaction of inhibitors of angiogenesis (6). Four percent of patients under sorafenib treatment and 8% of patients under sunitinib treatment develop arterial hypertension requiring intensive or combination therapy *(table 3)* (4, 5). The importance of checking blood pressure was documented in the licensing study, which reported that uncontrolled hypertension was the most important cause of a severe event during sorafenib treatment (5).

The development of hypertension during TKI treatment has not been adequately explained. It may be linked to increased fluid retention, increased peripheral resistance, stimulation of pressor receptors or even depletion of vascular nitric oxide (6, 15). There are no standard recommendations for treatment. It is recommended that blood pressure should be monitored by daily documentation, with early adjustment to normal values. It is usually possible to normalize blood pressure without dose adjustment *(table 5)*. The treatment-free interval during sequential therapy with sunitinib must be complied with. It may often be necessary to reduce antihypertensives as well.

Endocrinological adverse drug reactions

There was no routine evaluation of endocrinological parameters in the licensing studies. As a consequence, the interference of the drugs with thyroid function was initially only known anecdotally. There have now been several analyses – mostly retrospective – describing the importance of hypothyroidism primarily associated with sorafenib and sunitinib (11, 12, 16–18). This gave rise to a recommendation from the American Food and Drug Administration (FDA) that thyroid parameters should be controlled before treatment with sunitinib. As the number of cases is only small and some of the analyses have been retrospective, some prospective, there is great variability in the values given for the incidence of treatment-associated hypothyroidism *(table 3)*.

Changes in thyroid function, as measured in the laboratory, have been found for 34% to 84% of patients under treatment with sunitinib (11, 12, 16–18). This was thought to require treatment in 15% to 36% of patients and about half of the treated patients benefited from hormone substitution.

In the experience of the authors, routine monitoring of thyroid function is advisable for the early detection of hypothyroidism, as severe hypothyroidism may occur *(table 6)*. The underlying mechanism is a matter of speculation. Possibilities include a drug-induced immunological phenomenon, inflammation of the thyroid, inhibition of signaling pathways related to thyroid function (RET, rearranged during transfection protooncogene), and inhibition of the synthesis of thyroid hormone (6, 17). No final conclusion can be drawn about thyroid malfunction under sorafenib, as the data and their clinical relevance are controversial (19).

TABLE 4

Recommended supportive therapies for selected adverse drug reactions

Drug Reaction	Prophylaxis	When symptoms present	Accompanying tests	Dose reduction
Stomatitis Mucositis	Mouth rinses, e.g., sage tea or sodium chloride solution	Avoidance of acidic foods, dexpanthenol sugar-coated tablets, dexpanthenol cream, topical anesthetics, agents to protect the mucus membrane, topical steroids	If superinfection suspected, possibly take smear or throat rinse. Endoscopy for severe or persistent symptoms	If nutrition inadequate, possibly treatment-free interval and dose reduction by 12.5 mg or 200 mg
Hand-foot-skin-reaction	Relieve pressure on the affected parts, no excessive sport, skin care	Cooling hand or foot baths, lotions containing urea, steroid-containing external agents, possibly oral vitamin B6 preparations, possibly shoe inlays		Treatment-free intervals at grades 3 or 4 and dose reduction by 12.5 mg or 200 mg
Diarrhea	Avoidance of high roughage food	Mild forms: Ensure adequate hydration, possibly with motility inhibitor	Possibly exclusion of secondary causes	Treatment-free intervals and dose reduction at grades 3 or 4
Fatigue	Maintain physical and social activities	Possibly antidepressive	Exclude secondary causes: cardiomyopathy, hypothyroidism, anemia	Treatment-free intervals at grades 3 or 4 and possibly dose reduction by 12.5 mg or 200 mg
Xerosis cutis/ pruritus	Lubricating skin cream	Skin lotions containing urea (5% to 10%)		No treatment-free interval or dose reduction necessary
Nausea/ vomiting		Agents to protect mucous membranes, proton pump inhibitors, possibly dopamine antagonists, rarely serotonin antagonists		Treatment-free intervals at grades 3 or 4 and possibly dose reduction by 12.5 mg or 200 mg
Hypo-thyroidism	Measure changes in TSH	Possibly L-thyroxine substitution	Exclusion of other causes	No treatment-free interval or dose reduction necessary
Hypophos-phatemia	Electrolyte control	Alimentary substitution		No treatment-free interval or dose reduction necessary

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TSH, thyroid stimulating hormone

Hematological laboratory parameters

Changes in blood count mostly occur during treatment with sunitinib. 60% to 78% of treated patients exhibit leucopenia, neutropenia, lymphopenia, thrombopenia, or anemia. Grade 3 or grade 4 neutropenia occurs in 13% of patients and grade 3 or grade 4 thrombopenia in 8% of patients. A treatment-free interval is then necessary. In contrast, only 8% of patients treated with sorafenib exhibit anemia (4, 5). 13% of patients treated with sunitinib suffer nosebleeds. There is no adequate explanation for this.

36% of patients treated with sunitinib and 31% of patients treated with sorafenib exhibit hypophosphatemia (4, 5). This is an unusual side effect in tumor therapy; substitution is sometimes necessary.

Special features of combination and multimodal therapy

It is known that there may be increased tendency to bleed and impaired wound healing during treatment with bevacizumab, an anti-angiogenesis antibody. As a consequence, a treatment-free interval may be necessary before an operation (6, e7, e8). On the basis of the licensing studies, it is recommended that there should be a preoperative treatment-free interval of 14 days with sorafenib or sunitinib. Under these conditions, bleeding complications have only rarely been reported with these two substances, so that this procedure appears to be justified in routine clinical practice (4, 5).

Radiotherapy is an effective palliative therapy in advanced RCC. There are however no consistent data thus far on the combination of oral therapy with radiotherapy. This should therefore only occur within studies.

There are not yet any data on the use of the new substances in combination with bisphosphonates. However, no additional toxicity is to be expected, because of the disparate side effect spectra and metabolic pathways.

Conclusion

The use of tyrosine kinase inhibitors has made an essential contribution to progress in the treatment of renal cell carcinoma. The new substances give promising objective response rates and are better tolerated by most patients than immunotherapy with interferon alone. Extended access programs with a total of about 7500 patients have confirmed that these substances can be readily controlled and that they are safe under less well controlled conditions.

The recognition and management of the adverse reactions from this new generation of drugs is of great importance in directing tumor therapy. The most important adverse reactions are disturbances in blood

TABLE 5

Suggested therapy for arterial hypertension under tyrosine-kinase inhibitor therapy

RR	Treatment-Free Interval	Intervention	Control	Therapy
> 140/90 mm Hg*1	No	Control within 24 h	Introduction of antihypertensive therapy, accompanied by repeated measurements	Frequently monotherapy, e.g. Ca antagonist or β-Blocker
Severe Hypertension (systole > 200 mm Hg*2)	Yes	Changes monitored closely, rapid escalation with exhaustion of the single dose		Mostly combination therapy. For example, additional vasodilators, urapidil, central α-agonists or AT-II inhibitors. In resistant cases, multiple combinations necessary

*1 based on the 7th report of the JNC (20)
*2 Authors' recommendation

TABLE 6

Rational follow-up controls during molecular therapy with sunitinib or sorafenib

	Clinical	Endocrine	Laboratory	Imaging
From day 1	Blood pressure measurement, continuous			
Each month or course		TSH	Parameters for renal function, electrolytes, liver function, blood count	
Every second course or month				Ultrasound, X-ray, CT or MRI to evaluate tumor response

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TSH, thyroid stimulating hormone

pressure, in the skin and mucous membranes, and in thyroid function. In contrast to cytotoxic therapies, the adverse reactions are low grade, but persistent. Treatment can often only be successfully continued after timely intervention. In addition to the familiar side effects of oncological treatment, there are some unusual reactions, requiring special attention from the responsible physician.

It is expected that these drugs will be used increasingly for different tumors and that additional adverse reactions will then be identified. Although sorafenib and sunitinib are administered orally and severe toxicity is relatively rare, there is a wide spectrum of adverse effects, leading in some patients to massive impairment of the quality of life. All responsible physicians must therefore remain alert.

Conflict of interest statement
Dr. Ivanyi has received funding for traveling from Bayer Health Care.
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