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Experience with sorafenib and adverse event management

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Contents

Abstract

Sorafenib was the first multikinase inhibitor to be approved for use in renal cell cancer (RCC) in the US (2005) and in Europe (2006). In the Treatment Approaches in Renal Cell Cancer Global Evaluation Trial (TARGET), sorafenib showed a significant progression-free survival advantage over placebo in patients with advanced RCC. Incidence rates of adverse events were significantly higher with sorafenib than with placebo. Management of adverse events is an essential component of care to prevent negative impact on patient quality of life and dose modification of sorafenib therapy. This report, based on an expert panel discussion held in February 2009, presents recommendations for the management of skin rash, hand-foot skin reaction, diarrhea, and hypertension, and strategies to help lessen the frequency and severity of these events. In addition, general recommendations for dose modifications are discussed. The goal of these management recommendations is to optimize sorafenib therapy for advanced RCC.

Keywords: Sorafenib; Renal cell carcinoma; Adverse events; Hand-foot skin reaction; Diarrhea; Hypertension

1. Introduction

Although renal cell cancer (RCC) represents only 2–3% of all cancers, this disease has considerable global impact [1]. In the European Union (EU) and the United States (US),

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between 46,000 and 63,000 new cases of RCC are diagnosed annually, and approximately 40% of RCC patients die from RCC-related causes each year [2,3].

While localized disease is curable by surgery, metastatic and locally advanced disease are considerably more difficult to treat [4,5]. Historically, therapeutic options for metastatic or for locally advanced RCC, primarily cytokine therapy, produced low response rates and considerable toxicity [6–9]. Until recently, no other treatment options were available to patients who were nonresponsive to or intolerant of cytokine therapy [10].

Sorafenib (Bayer HealthCare Pharmaceuticals, Inc., Wayne, NJ and Onxy Pharmaceuticals, Inc., Emeryville, CA) was the first multikinase inhibitor to be approved for use in RCC in the US (2005) and in Europe (2006). Sorafenib is an oral, biaryl urea RAF kinase inhibitor that acts against both vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptors, simultaneously targeting both tumor cell proliferation and angiogenesis [6,11–13].

In the phase III Treatment Approaches in Renal Cell Cancer Global Evaluation Trial (TARGET), sorafenib showed a statistically significant progression-free survival (PFS) advantage over placebo in the treatment of patients with metastatic RCC who had progressed after one systemic treatment (5.5 months vs. 2.8 months; $P < 0.001$) [10]. In addition, 10% of patients receiving sorafenib experienced partial responses to therapy, compared with 2% of patients receiving placebo ($P < 0.001$) [10].

In general, sorafenib is a well tolerated drug. In the TARGET trial, the rates of early therapy discontinuation in the active treatment and placebo arms were comparable (10% vs. 8%, respectively) [10]. Skin toxicities, diarrhea, and hypertension were the most frequent adverse reactions of clinical importance in sorafenib-treated patients (Table 1) [10]. Expanded access studies of sorafenib in advanced RCC in North America (NA-ARCCS) and Europe (EU-ARCCS) substantiated the safety prolife of sorafenib in the clinical setting (Table 1) [14,15].

The adverse reactions associated with sorafenib therapy are often manageable with ancillary treatments and dose modification. Nonetheless, as with any agent, some patients experience adverse events with potential impact on physical, psychological, or social health. These issues may lead to drug discontinuation or dose reduction that can diminish potential life-prolonging benefits of sorafenib [12,16]. Understanding and implementation of management strategies for adverse reactions are essential to optimize sorafenib treatment.

This expert opinion captures the experience of an expert panel of treating physicians who have managed patients through common adverse events seen with sorafenib. Members of the expert panel were selected based on their extensive clinical experience with sorafenib in the treatment of patients with RCC and were gathered from the United States and Abroad on February 26, 2009, in Orlando, FL, to share their recommendations for monitoring and treating patients with sorafenib-induced skin toxicities, diarrhea, and hypertension.

2. Skin toxicities

Treatment-related skin toxicities associated with sorafenib have included rash/desquamation, hand-foot skin reaction (HFSR), alopecia, and pruritus in the TARGET clinical trial and the NA-ARCCS and EU-ARCCS expanded access studies (Table 1) [10,14,15]. The vast majority (81–98%) of patients reporting these adverse drug reactions experienced mild to moderate (grade 1–2) symptoms (Tables 1 and 2) [10,14,15]. Grade 3–4 adverse drug reactions were reported infrequently for pruritus (<1%), alopecia (<1%), rash/desquamation (1–5%), and HFSR (6–12%) [10,14,15]. Here, we will discuss the management of sorafenib-induced HFSR and rash.

2.1. Hand-foot skin reaction

Hand-foot skin reaction is characterized by the formation of thick, discrete hyperkeratotic lesions that affect pressure points, such as fingertips and heels, and flexure areas, such as the interphalangeal and metacarpal-phalangeal joints (Fig. 1) [12,17]. Lesions typically develop within the first 2–4 weeks of sorafenib treatment and are often painful, which can significantly affect patient quality of life by limiting mobility and disrupting the activities of daily living [4,12,17].

The results of a recent meta-analysis suggest that HFSR may be more prevalent in patients with RCC treated with sorafenib than in patients with other cancers (including melanoma, non-small-cell lung cancer, prostate cancer, hepatocellular carcinoma, non-gastrointestinal stromal tumor sarcoma, and neuroendocrine tumor) treated with sorafenib [17]. In this meta-analysis, the incidence of HFSR (all grades) occurring in 4883 patients with various cancer types treated with sorafenib in 11 clinical trials was 33.8% (95% CI: 24.5–44.7%), but in patients with RCC, the incidence of

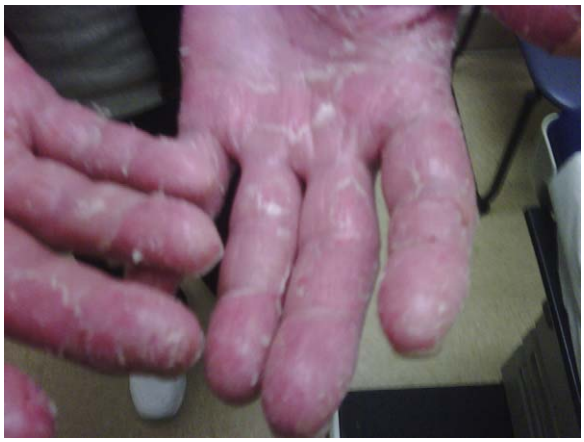

Fig. 1. Hand-foot syndrome in a patient receiving sorafenib.

Table 1
Summary of adverse events occurring in ≥10% of patients with metastatic RCC treated with sorafenib in select clinical studies[a].

Adverse event	Randomized controlled study		Expanded access studies			
	TARGET[b] (*N* = 451)		NA-ARCCS[a] (*N* = 2504)		EU-ARCCS[a] (*N* = 1031)	
	All grades (%)	Grade 3/4 (%)	Grade 2 (%)	Grade ≥3 (%)	All grades (%)	Grade 3/4 (%)
Cardiac						
Hypertension	17	4	8	5	14	4
Constitutional						
Fatigue[c]	37	5	7	5	34	8
Weight loss	10	<1	2	<1	10	1
Dermatologic						
Rash or desquamation	40	1	9	5	29	5
Hand-foot skin reaction	30	6	9	10	47	12
Alopecia	27	<1	2	<1	28	<1
Pruritus	19	<1	ND	ND	11	0
Gastrointestinal						
Diarrhea	43	2	6	2	43	5
Nausea[c]	23	<1	4	1	17	1
Anorexia[c]	16	<1	5	1	22	3
Vomiting[c]	16	1	2	1	11	1
Oral mucositis	ND	ND	2	1	26	3
Neurologic						
Sensory neuropathy	13	<1	ND	ND	ND	ND
Pain						
Headache	10	<1	ND	ND	ND	ND

NA-ARCCS, North American Advanced Renal Cell Carcinoma Sorafenib expanded access study; EU-ARCCS, European Advanced Renal Cell Carcinoma Sorafenib expanded access study; ND, no data.

[a] Adverse event data collected for the NA-ARCCS and EU-ARCCS studies used methodology different from that used in the TARGET study; thus, the data should not be directly compared.

[b] Occurring at a significantly higher rate than in the placebo group, unless otherwise indicated.

[c] Incidence rate not significantly different from that in the placebo group in the TARGET study.

Table 2
Common terminology criteria for adverse events version 3.0 toxicity scale for common adverse events associated with sorafenib therapy: dermatologic adverse events, diarrhea, and hypertension.

Adverse event	Grade	Clinical characteristics
Rash/desquamation	1	Macular or papular eruption or erythema without associated symptoms
	2	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA)
	3	Severe, generalized erythroderma or macular, papular, or vesicular eruption; desquamation covering ≥50% BSA
	4	Generalized exfoliative, ulcerative, or bullous dermatitis
Rash/acneiform	1	Intervention not indicated
	2	Intervention indicated
	3	Associated with pain, disfigurement, ulceration, or desquamation
Hand-foot skin reaction	1	Minimal skin changes or dermatitis (e.g., erythema) without pain
	2	Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function
	3	Ulcerative dermatitis or skin changes with pain interfering with function
Diarrhea	1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared with baseline
	2	Increase of 4–6 stools per day over baseline; IV fluids indicated <24 h; moderate increase in ostomy output compared with baseline; not interfering with activities of daily life
	3	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 h; hospitalization; severe increase in ostomy output compared with baseline; interfering with activities of daily life
	4	Life-threatening consequences (e.g., hemodynamic collapse)
Hypertension	1	Asymptomatic, transient (<24 h) increase by >20 mm Hg (diastolic) or to >150/100 mm Hg if previously within normal limits; intervention not indicated
	2	Recurrent or persistent (≥24 h) or symptomatic increase by >20 mm Hg (diastolic) or to >150/100 mm Hg if previously within normal limits; monotherapy may be indicated
	3	Requiring more than one drug or more intensive therapy than previously
	4	Life-threatening consequences (e.g., hypertensive crisis)

Table 3
Management recommendations for rash/desquamation and hand-foot skin reaction associated with sorafenib therapy.

	Management recommendations	
	Rash/desquamation	Hand-foot skin reaction
Prevention	• Use zinc oxide-based emollients or lanolin-based creams	• Perform physical exam to identify preexisting hyperkeratotic areas of the body • Use lanolin-based creams or urea-based lotions • Avoid exposure to hot water, excessive friction on the skin or pressure on the feet, and vigorous activities that unduly stress the hands and feet
Mild to moderate	• Use zinc oxide-based emollients or lanolin-based creams • Use colloidal oatmeal lotion to treat pruritus • Wear protective clothing, such as long-sleeved shirts, gloves, thick socks, and insoles	• Use lanolin-based creams or urea-based lotions in conjunction with gloves, socks, or occlusion bandages overnight • Consider reducing dose until symptoms subside
Moderate to severe	If occurring in the first few weeks of therapy: • Reduce dose until symptoms subside • Re-escalate to full dose if tolerated If symptoms persist or recur: • Interrupt dosing until symptoms subside • Restart at reduced dose • Re-escalate to full dose if tolerated	If occurring in the first few weeks of therapy: • Reduce dose until symptoms subside • Re-escalate to full dose if tolerated If occurring after 6–8 weeks of therapy: • Interrupt dosing until symptoms subside • Restart at reduced dose • Re-escalate to full dose if tolerated

HFSR was greater than in those with other tumors (42.0% vs. 27.6%, respectively). The incidence of grade 3 or 4 HFSR, however, remained similar regardless of tumor type (8.9% vs. 9.1%, respectively) [17]. The biological basis for the disparity in HFSR incidence between RCC and non-RCC patients treated with sorafenib is not known.

Because the incidence of HFSR may be higher in RCC patients treated with sorafenib than in patients with other tumor types, monitoring for and management of this adverse event in the RCC patient population takes on added importance. Even before sorafenib treatment is started, several preventive strategies should be implemented to reduce the risk of developing HFSR (Table 3). Patients should be advised to address preexisting hyperkeratotic areas by using lanolin-based or urea-based lotions and having calluses removed from the feet [12]. In this regard, prophylactic podiatric care should be strongly considered. Avoidance of exposure to hot water, excessive friction on the skin or pressure on the feet, and vigorous activities that unduly stress the hands and feet are also recommended. Based on our clinical experience, clinicians should be aware that HFSR can occur at other body sites (e.g., inguinal region, penis, vulva, nose, ears, and breasts) and not overlook this possibility in patients with HFSR symptoms at sites other than the hands and feet.

Mild cases of HFSR with minimal buildup of keratin at pressure points of the hands and feet can be managed with the use of lanolin-based or urea-based lotions. Cotton gloves, socks, or an occlusion bandage can provide additional relief when used with lotion and provide protection from further skin trauma [12]. In our experience, moderate to severe cases of HFSR that develop in the first few weeks of sorafenib therapy can be managed with dose reduction. Once the symptoms of HFSR have subsided, if the patient remains stable at or responds to the reduced dose, then dose escalation may be implemented gradually, with careful monitoring for recurrence of symptoms. For moderate to severe cases that emerge after 6–8 weeks of sorafenib therapy, however, dose interruption is recommended until skin symptoms improve. Then, sorafenib can be restarted at a reduced dose and gradually escalated to the full dose (Table 3).

2.2. Rash

Patients receiving sorafenib may experience more than one type of rash [18]. Generally, rashes will develop within the first treatment cycle but can develop in subsequent cycles. The onset of rash is often acute and characterized by erythema of the face and scalp, macular and papular eruptions, desquamation, and sometimes pruritus [16,18]. In our experience, erythematous rash appears to occur more commonly in women than in men and particularly in women of Asian background. The biological rationale for this apparent gender and ethnic bias is not known, but we speculate that it may be related to the relative dose received with respect to body surface area or effects on drug metabolism.

Skin rash has been observed in patients receiving epidermal growth factor receptor (EGFR) inhibitor-targeted therapies. Although 40% of patients in the TARGET trial reported rash/desquamation, skin rash is more commonly reported by patients receiving treatment with an EGFR inhibitor—75% with erlotinib (Genentech, Inc., South San Francisco, CA and OSI Pharmaceuticals, Inc., Melville, NY) and 89% with cetuximab (Bristol-Myers Squibb Company, Princeton, NJ and ImClone Systems Incorporated, Branch-

Table 4
Comparison of skin toxicities associated with select tyrosine kinase inhibitors.

Tyrosine kinase inhibitor	Molecular target(s)	Approved indication(s)	Description of associated skin toxicities
Cetuximab [36]	EGFR	First-line and second-line metastatic CRC; first-line and second-line SCCHN	Acneiform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (e.g., *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis, and cheilitis, and hypertrichosis)
Erlotinib [37]	EGFR	Second-line advanced NSCLC; first-line advanced pancreatic cancer	Typically erythematous and maculopapular rash, acne with follicular pustules, desquamation; associated symptoms may include itching, tenderness and/or burning; dry skin with or without digital skin fissures may occur
Gefitinib [38,39]	EGFR	First-line and second-line NSCLC	Papulopustular eruption; less commonly xerosis, folliculitis, paraonychia, alopecia, vasculitis
Sorafenib [12,24]	VEGFR, PDGFR	Advanced RCC	Erythematous, macular, papular skin rash, often with desquamation; hand-foot skin reaction; less commonly pruritus; facial erythema, scalp dysthenia, alopecia, and subungual splinter hemorrhages, keratoacantoma or squamous cell carcinoma, stomatitis
Sunitinib [12,40]	VEGFR, PDGFR, KIT, FLT-3, CSF-1R, RET	Advanced GIST and advanced RCC	Seborrheic dermatitis-like rash, dry skin, acral erythema, pruritus, stomatitis, subungual splinter hemorrhages, alopecia, modifications of hair growth or pigmentation, skin discoloration, and hand-foot skin reaction

EGFR, epidermal growth factor receptor; VEGFR, vascular endothelial growth factor receptor; PDGFR, plate-derived growth factor receptor; KIT, stem cell factor receptor; FLT-3, Fms-like tyrosine kinase 3; CSF-1R, colony stimulating factor receptor type 1; RET, neurotrophic factor receptor; CRC, colorectal cancer; SCCHN, squamous cell carcinoma of the head and neck; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma; GIST, gastrointestinal stromal tumor.

burg, NJ) [19,20]. Skin toxicities induced by EGFR inhibitor therapy overlap with those induced by sorafenib, with some differences. Skin toxicities associated with EGFR inhibitors are characterized by alopecia, modifications in skin pigmentation, and skin dryness and fissuring (Table 4). The ability to distinguish between the characteristic skin manifestations will enable the treating physician to more accurately diagnose, treat, and manage adverse reactions of drug treatment.

For desquamating rashes associated with sorafenib therapy, the use of zinc oxide-based emollients or lanolin-based creams may help to prevent the development of skin problems. The use of emollients and creams can also treat mild cases of rash. Pruritus associated with rash may be treated with colloidal oatmeal lotion, which has been shown to effectively alleviate rash symptoms induced by other targeted agents [21]. More generally, patients should be advised to protect skin surface areas by wearing long sleeves, gloves, thick socks, or insoles (Table 3).

To manage an inflammatory erythematous rash that develops within the first week of sorafenib therapy, dose interruption or dose reduction is recommended to allow the skin reaction to subside. Once recovered, if sorafenib was temporarily discontinued, therapy can be restarted at a reduced dose, typically at half the starting dose, or 400 mg once daily. If the patient tolerates the reduced dose, then dose escalation can be undertaken to reach the full dose (Table 3). Reinstitution of sorafenib is usually well tolerated and escalation of the dose to the original level is frequently achieved.

2.3. Other skin reactions

Case reports of patients developing keratoacanthoma, actinic keratoses, or squamous cell carcinoma (SCC) while on sorafenib have been described in the literature (Fig. 2) [22–26]. In light of these reports, Bayer HealthCare Pharmaceuticals performed a complete review of clinical safety data from sorafenib clinical trials and marketed use and found keratoacanthoma and SCC to be an uncommon event, occurring in between 1/1000 and 1/100 patients receiving sorafenib [27]. Although uncommon, the development of keratoacan-

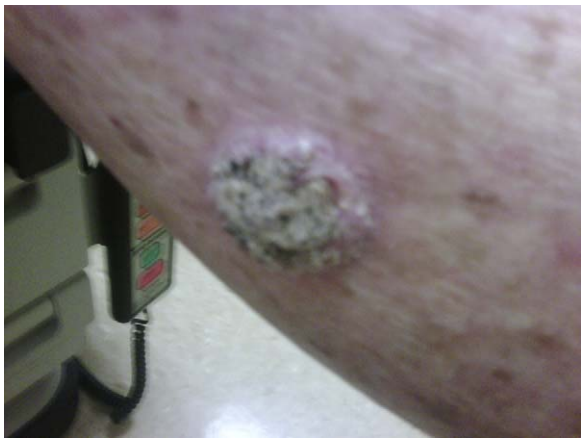

Fig. 2. Keratoacanthoma in a patient receiving sorafenib.

Table 5
Management recommendations for diarrhea associated with sorafenib therapy.

	Management recommendations
Prevention	• Take loperamide (2 mg) 30 min before scheduled dose of sorafenib
Mild to moderate	• Increase dietary intake of high-fiber, bulking foods, such as bananas, rice, apples, and toast • Add dietary supplements, such as: ◯ Soluble fiber ◯ Pectin, 1 teaspoon daily • Take loperamide after each loose bowel movement • Take diphenoxylate hydrochloride/atropine sulfate (5 mg) • Take cholestyramine (4 mg thrice daily) but not within 1–2 h before or after scheduled dose of sorafenib
Moderate to severe	• Interrupt dosing until symptoms subside • Restart at reduced dose • Re-escalate to full dose if tolerated

thoma or SCC is undesirable, so timely recognition of these conditions and referral to a dermatologist of suspected lesions are recommended for early intervention and prevention of morbidity in patients receiving sorafenib.

3. Diarrhea

In the TARGET trial, diarrhea (all grades) occurred in 43% of patients receiving sorafenib, compared with 13% of patients receiving placebo [10]. Diarrhea of grade 3 or 4 severity was reported in 2% of patients receiving sorafenib and 1% of patients receiving placebo (Tables 1 and 2) [10]. Although severe bouts of diarrhea are uncommon with sorafenib therapy, treatment-related diarrhea can be persistent. Onset of symptoms may be gradual, but the diarrhea can continue for the duration of sorafenib therapy. Rarely, patients may experience periodic episodes of catastrophic diarrhea while on sorafenib. Even mild to moderate diarrhea can significantly affect quality of life by impairing mobility and independence. Thus, attention to diarrhea is important.

Loperamide (2 mg), taken about 30 min before the scheduled dose of sorafenib, is one preventive measure for sorafenib-induced diarrhea (Table 5) [28]. For mild cases of diarrhea, dietary changes can provide relief: increasing the intake of fiber-rich foods, such as bananas, rice, apples, and toast, may help to relieve symptoms [28]. Dietary supplements, such as those containing psyllium dietary fiber, or pectin, taken as a supplement (1 teaspoon daily), may also act as bulking agents and alleviate symptoms (Table 5). For mild to moderate diarrhea, a dose of loperamide may be taken after each loose bowel movement. If symptoms persist, diphenoxylate hydrochloride/atropine sulfate (5 mg) may also be used [28]. In our experience, cholestyramine (4 g three times daily) may be effective in alleviating diarrhea for some patients, but because this agent can bind to other drugs [29], it should not be taken within 1–2 h before or after dosing with sorafenib.

For moderate to severe cases of diarrhea, a dose interruption is recommended (Table 5). Based on our experience, a 5- to 7-day interruption in sorafenib therapy is usually sufficient to allow the patient's body to re-equilibrate. Then, sorafenib therapy can be restarted at a reduced dose and gradually escalated to the full dose.

4. Hypertension

Hypertension is an adverse event associated with tyrosine kinase inhibitors and other angiogenesis inhibitors, such as sorafenib, sunitinib (Pfizer Inc., New York, NY), and bevacizumab (Genentech, Inc., South San Francisco, CA), and appears to be a class-type side effect of these drugs [30]. While the biological mechanisms underlying the development of hypertension with angiogenesis inhibitors are unknown, several hypotheses have been advanced. Hypertension in this setting may involve a reduction in the number of small peripheral blood vessels (e.g., capillaries and arterioles) caused by anti-angiogenic agents. This, in turn, can decrease peripheral vascular surface area and increase vascular resistance [16]. In addition, sorafenib may also directly impact angiotensin-II-mediated blood pressure control by interfering with angiotensin-II-dependent activation of tyrosine kinase receptors, including PDGFR [31].

In the TARGET clinical trial and the NA-ARCCS and EU-ARCCS expanded access studies, hypertension (all grades) was reported in 14–17% of patients, with 4–5% of cases of grade 3 or 4 severity [10,14,15]. In a study of sorafenib in advanced hepatocellular carcinoma ($N = 297$ receiving sorafenib vs. $N = 302$ receiving placebo), the incidence of hypertension (all grades) was 5% in patients receiving sorafenib, with 2% of cases of grade 3 severity [32]. These rates of hypertension are comparable to that observed with other angiogenesis inhibitors, such as sunitinib and bevacizumab for RCC and other tumor types [33,34]. Nonetheless, because uncontrolled hypertension can contribute to the onset of cardiovascular events (Table 2), recognizing and managing hypertension in sorafenib-treated patients is an important component of patient care.

Before the start of sorafenib therapy, patients should be advised to seek treatment to control preexisting hypertension (Table 6). Increases in blood pressure may arise as early as the first 3 weeks of sorafenib therapy and persist for as many as 18 weeks before leveling off [35]. Mean systolic and diastolic pressures in groups of patients were observed to increase by 16% and 11%, respectively [35]. For patients with preexisting hypertension, we recommend managing cases of mild to moderate increases in blood pressure by increasing the dose of their current anti-hypertensive medication or adding a new anti-hypertensive medication (Table 6). A referral to the primary treating physician may not be necessary. In cases where patients without preexisting hypertension

Table 6
Management recommendations for hypertension associated with sorafenib therapy.

	Management recommendations
Prevention	• Control preexisting hypertension
Mild to moderate	• Manage according to standard medical practice • Take anti-hypertensive medication (monotherapy), if necessary
Moderate to severe	• Increase dose of anti-hypertensive medication • Add second hypertensive medication, if necessary • Consider dose interruption or discontinuation of sorafenib if hypertension is severe, persistent, or does not respond to anti-hypertensive medication

develop blood pressure elevations on sorafenib, we recommend that an anti-hypertensive medication be added to their treatment regimen and patients be managed according to standard medical practice. Coordination with the primary care physician in these cases may be desirable. In cases of severe or persistent hypertension that do not respond to anti-hypertensive drug treatment, dose interruption or discontinuation may be necessary (Table 6) [27].

5. Dose modifications

Most adverse reactions associated with sorafenib therapy are mild and can be managed without dose adjustment. On occasion, patients on sorafenib therapy will experience adverse reactions that are severe, chronic, or do not respond well to treatment. Although dose modification of sorafenib therapy may be necessary for relief from adverse reactions, interruption or discontinuation of sorafenib can diminish the therapeutic benefit of this drug. Optimizing control of adverse reactions while maintaining therapeutic doses of sorafenib to the greatest extent possible is the goal of therapy.

When dose reductions become necessary, reducing the sorafenib dose to 400 mg once daily until symptoms of adverse reactions subside is often adequate [27]. If further dose reductions are necessary, the dose can be reduced to 400 mg once every other day (Table 7) [27]. Once symptoms of adverse reactions abate, then the sorafenib dose can be escalated to the full dose. Based on our clinical experience, we suggest that dose escalation occur in a gradual manner, based on individual patient response to dose increases of 200 mg per day for several days until the full dose of 400 mg twice daily is reached. If a patient's cancer responds to or remains stable at a reduced dose, then we recommend that dose escalation be undertaken at a gradual pace with an eye to maintaining greater control over adverse reaction symptoms. In this situation, a patient can remain at the reduced dose as long as imaging studies show that the patient's cancer remains stable, and re-escalation of the dose should be considered when there is identifiable progression of the RCC.

Table 7
Recommendations for dose modifications of sorafenib based on prescribing information and author clinical experience.

	Dose modifications
Dose reduction	• Reduce dose to 400 mg once daily until symptoms subside • If symptoms persist for >7 days, then reduce dose to 400 mg once every other day
Dose escalation	• If patient's cancer is unstable, then increase dose by 200 mg per day for several days until the full dose of 400 mg twice daily is reached • If patient's cancer is stable, then dose escalation can be delayed as long as imaging studies show stable cancer
Restart after dose interruption	• Restart at a reduced dose (dose dependent on tumor status), and increase dose gradually until the full dose of 400 mg twice daily is reached

Data on the efficacy of sorafenib given at doses lower than the standard dose (400 mg twice daily) are limited. In a series of phase I studies, sorafenib dosing at various schedules (ranging from 50 mg daily to 800 mg twice daily on a schedule of 7 days on/7 days off, 21 days on/7 days off, 28 days on/7 days off, or continuous dosing) were explored in a total of 137 patients with various solid tumors [41]. No clear dose-response relationship was observed in any of the four trials, although antitumor activity was more likely in patients who had received $\geq$200 mg twice daily [41].

In the case of severe or persistent skin toxicities, severe or persistent hypertension that does not respond to anti-hypertensive medications, hemorrhage that requires medical intervention, intractable diarrhea, or the occurrence of cardiac ischemia or infarction, then temporary or permanent discontinuation of sorafenib therapy may be considered. If discontinuation is temporary, then sorafenib therapy can be restarted at a reduced dose that is dependent on the tumor status and escalated gradually according to clinical judgment, utilizing guidelines described above (Table 7) [27].

6. Conclusions

Sorafenib was the first multikinase inhibitor to be approved for use in RCC in the US (2005) and in Europe (2006). In clinical study, sorafenib has been shown to significantly prolong PFS, compared with placebo. Skin toxicity, diarrhea, and hypertension are clinically important adverse reactions of treatment requiring clinical attention in some patients. In the majority of patients presenting with mild to moderate symptoms, minor interventions are warranted, including dietary or lifestyle changes, podiatric attention, and over-the-counter remedies. For more severe, persistent, or unresponsive symptoms, dose reduction or interruption

may be necessary to allow symptoms to abate. After symptoms subside, sorafenib therapy can usually be restarted or escalated back to reach the full dose. In only a small number of cases, permanent discontinuation of sorafenib may be warranted. As the delivery of healthcare becomes more individualized to each patient, biomarker tools may become available that can predict response to specific therapies, thus sparing those who are not likely to benefit from therapy from treatment-related toxicities. Until that potential is realized, fostering greater understanding of the adverse reactions associated with sorafenib therapy, active monitoring for adverse reactions, and careful management of specific side effect patterns will ensure that patients reap the greatest benefits of sorafenib therapy.

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