

Managing the side effects of sorafenib and sunitinib

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The approval of sorafenib and sunitinib has created a paradigmatic shift in the treatment of metastatic renal cell carcinoma. However, there is a need for effective patient education and early intervention to manage side effects. This article offers a brief overview of the side effects associated with sorafenib and sunitinib as well as guidelines for helping patients resolve their symptoms and a **patient education resource box on page 562**.

The US Food and Drug Administration's approval of sorafenib (Nexavar) and sunitinib (Sutent) represents a significant advance in the treatment of advanced renal cell cancer. Sorafenib and sunitinib are self-administered, so it's crucial to educate patients and those who may assist them on the **recommended dose and schedule:**

Sorafenib

- Given as a 200-mg tablet at a starting dose of 400 mg, twice daily on a continuous schedule
- Should be given on an empty stomach, 1 hour before meals or 2 hours after
- Should be reduced to 400 mg daily if dose modification is needed.

Sunitinib

- Given at a starting dose of 50 mg daily for 28 days followed by a 14-day rest period
- Should be reduced to 37.5 mg daily, then to 25 mg daily if dose modification is needed
- Is available in capsule strengths of 50, 25, and 12.5 mg, making dose modification relatively simple.

Ideally, patients should receive written information about these drugs and their side effects, including interaction with prescription and over-the-counter medications since cancer patients tend to use multiple drugs. Providing information about the mechanism of action for these drugs in simple terms helps patients understand how these multi-targeted therapies differ from chemotherapeutic and biologic response modifiers. And written instructions on dosing and drug administration facilitate adherence to treatment regimen.

Side effects

Table 1 lists the top 13 side effects for sorafenib and sunitinib, demonstrating the similarities and dif-

ferences in toxicity profile for the two drugs. Information on the etiology and management of treatment-induced hypertension and hand-foot syndrome is increasing, although no treatment algorithms for drug-related toxicities exist, and management of side effects is variable. The dermatologic side effects associated with these agents are unlike those of epidermal growth factor receptor (EGFR) inhibitors, and the presentation of dermatologic side effects is different for each drug. Both drugs are metabolized via the cytochrome P-450 pathway (CYP450), making drug interactions possible.

KEY POINTS

The FDA recently approved sorafenib and sunitinib, two targeted therapies for advanced renal cancer. Sunitinib was also approved for imatinib-refractory GIST.

Sorafenib and sunitinib may cause significant side effects that must be carefully managed, including fatigue, hypertension, diarrhea, mucositis, skin conditions, and hair changes.

Effective patient education is critical, since sorafenib and sunitinib are self-administered agents.

Nurses can help patients cope with gastrointestinal, dermatologic, hematologic, and cardiac toxicities.

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How these drugs work

SORAFENIB AND SUNITINIB are tyrosine kinase inhibitors that target two different signaling pathways, significantly interfering with the processes necessary for tumor cell proliferation. One pathway is VEGF—vascular endothelial growth factor—which plays a critical role in the proliferation, migration, and survival of endothelial cells involved in angiogenesis. Inhibition of VEGF interferes with the formation of new blood vessels that feed tumors. The second pathway is PDGF—platelet-derived growth factor. In blocking PDGF, sorafenib and sunitinib interfere with the formation of pericytes, leading to disruption in the stability and maturation of existing blood vessels around tumor cells. Sorafenib also interferes with tumor cell proliferation by inhibiting the raf-kinase pathway.

It's important to tell patients they should notify their oncologist or nurse when side effects are first noticed. Early intervention can decrease the severity of symptoms and maximize both treatment efficacy and quality of life. Treatment delays and dose reductions may limit clinical outcome and may have a negative impact on patients' ability to work and maintain social activities. Telephone interactions and assessments with healthcare professionals can determine whether the side effects require clinical evaluation.

Fatigue

Fatigue is a common complaint among patients receiving sunitinib and sorafenib, although its impact on quality of life is variable. Most patients can maintain their normal activity with minor modifications. For some patients, fatigue improves as treatment of the underlying disease begins to resolve symptoms. For others, treatment interruption or dose modification may reduce fatigue. Erythrocyte growth factors and nutritional intake are important considerations when evaluating and treating

disease-related fatigue. They can improve anemia, patients' quality of life, and their ability to continue treatment at the desired dose. Disease- and treatment-related anorexia, cachexia, and resulting weight loss should be monitored closely. Consult with a dietician about initiating oral supplements and ways to minimize the effects of anemia.

Encourage patients to:

- Stay as active as possible, as that will help them sleep better.
- Maintain normal work and social schedules.
- Take breaks as needed.
- Tell the doctor or nurse if they cannot tolerate activity or if their fatigue worsens so that appropriate treatment decisions can be made.

Hypertension

Hypertension may develop within the first few weeks of therapy or slowly over time. The exact etiology of hypertension is unclear, but it may be the result of pressor stimulation responses, increasing extracellular volume, and/or decreasing vascular compliance.¹ Decreased density of microvessels leading to increased peripheral vascular resistance or reduced bioavailability of nitric oxide may result in disruption of angiogenesis and then hypertension.² There may also be an association between therapy-induced hypertension and proteinuria.³ Although clinical trials continue to investigate the etiology of hypertension, effective management is critical to minimizing long-term sequelae of treatment-induced hypertension.

Nonpharmacologic strategies

- Advise your patients to make healthy lifestyle choices, including regular exercise, weight control, moderate alcohol consumption, and sodium restriction (less than 2 g/d).
- Instruct patients to take their own blood pressure weekly.
- Give them systolic and diastolic threshold numbers to use as a trigger for notifying healthcare professionals for early assessment and intervention.
- Suggest to your patients that they

TABLE 1

Comparison of side-effect profiles for sorafenib and sunitinib*

Side effect	Sorafenib (all grades)	Sunitinib (all grades)
Fatigue	37%	74%
Diarrhea	43%	55%
Nausea	23%	54%
Mucositis/stomatitis	–	53%
Dyspepsia	–	46%
Altered taste	–	43%
Anorexia	16%	31%
Rash/desquamation	–	40%
Hand-foot skin reaction	30%	–
Alopecia	27%	–
Pruritus	19%	–
Hypertension	17%	28%
Dyspnea	14%	28%

* Based on package insert for sorafenib and sunitinib

keep a diary of blood pressure measurements to help them adhere to treatment and communicate better with the healthcare team.

Pharmacologic strategies

- Prescribe antihypertensive agents, classified according to their mechanism of action (Table 2).⁴⁻⁶

Diarrhea

Changes in bowel habits and stool consistency are common for patients receiving sunitinib and sorafenib. Assess baseline bowel habits and stool consistency to recommend an intervention.

Dietary management for diarrhea

- Adding bananas and rice to the diet can help increase stool consistency.
- Fruit or vegetable juices are an important part of a well-balanced diet and do not appear to aggravate diarrhea when taken in normal quantities.
- Bulking and antidiarrheal agents such as Benefiber or Metamucil (psyllium) may also increase stool consistency and reduce the frequency of bowel movements.

TABLE 2

Antihypertensive medications

Class	Drug	Dose (mg)	Frequency	Action
Thiazide diuretics	HCTZ	12.5–50	qd	Decrease the rate of sodium and chloride reabsorption in the distal renal tubules
	Chlorthalidone	12.5–25	qd	
	Indapamide (Lozol)	1.25–5.0	qd	
Loop diuretics	Furosemide (Lasix)	20–80	bid	Inhibit reabsorption of sodium chloride in proximal and distal tubules and the loop of Henle
	Bumetanide (Bumex)	0.5–2.0	qd	
	Torsemide (Demadex)	20	qd	
Beta blockers	Atenolol (Tenormin)	25–100	qd	Decrease cardiac contractility, reduce heart rate, and inhibit renin release; may prevent second heart attack and heart failure
	Metoprolol (Lopressor)	50–200	bid	
	Metoprolol ER (Toprol XL)	50–200	qd	
	Propranolol (Inderal)	40–60	bid	
Alpha blockers	Carvedilol (Coreg)	12.5–50	bid	Decrease cardiac and beta blockers' output, reduce peripheral vascular resistance, increase vasodilation, decrease plasma renin activity
	Labetalol (Normodyne, Trandate)	200–800	bid	
ACE inhibitors	Ramipril (Altace)	2.5–20	qd	Suppress the renin-angiotensin-aldosterone system; prevent the conversion of angiotensin I to angiotensin II, resulting in decreased peripheral resistance and decreased aldosterone secretion
	Enalapril (Vasotec)	5–40	qd–bid	
	Benazepril (Lotensin)	10–40	qd	
	Fosinopril (Monopril)	10–40	qd	
	Captopril (Capoten)	25–50	tid	
ARBs	Valsartan (Diovan)	80–320	qd–bid	Block vasoconstricting and aldosterone-secreting effects of angiotensin II
	Losartan potassium (Cozaar)	25–100	qd–bid	
	Irbesartan (Avapro)	150–300	qd	
	Candesartan (Atacand)	8–32	qd	
	Olmesartan medoxomil (Benicar)	20–40	qd	
Ca-channel blockers	Diltiazem (Cardizem, Tiazac)	120–540	qd	Inhibit the blockers' inward flow of (nondihydropyridines) calcium into cardiac and smooth muscle cells, leading to arterial and coronary vasodilation and decreased contractility
	Verapamil (Calan, Covera)	120–480	qd	
Ca-channel blockers (dihydropyridines)	Nifedipine (Procardia, Adalat)	30–90	qd	
	Amlodipine (Norvasc)	2.5–10	qd	
	Felodipine (Plendil)	2.5–20	qd	

ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers; Ca-channel = calcium channel

■ Loperamide (Imodium) and diphenoxylate (Lomotil) should be initiated on a prn basis.

Anecdotal patient reports have indicated that the use of loperamide 30 minutes prior to meals can significantly reduce diarrhea after eating. Patients should be provided treatment options and encouraged to find the regimen that works best for them. Clinical guidelines may be beneficial in the management of diarrhea associated with these therapies.⁷

Note: Patients taking stool softeners or laxatives for constipation should be reminded to decrease or discontinue their use when no longer needed.

Gastrointestinal complaints

Patients taking sorafenib or sunitinib may experience dyspepsia, belching, flatulence, or bloating during therapy. Some recommendations are:

- Minimize gas-producing foods such as beans and bulky vegetables.
- Avoid carbonated beverages.
- Use antacids and acidophilus products such as some yogurts and cheeses, which may reduce symptoms.

A few cautions about drug interactions: Note that while histamine receptor-blocking agents (such as famotidine and ranitidine) or proton pump inhibitors (such as lansoprazole) may be useful in controlling gastrointestinal problems, they should not be taken within

2 hours of receiving sorafenib or sunitinib, as they can interfere with drug absorption and metabolism.

You should monitor potential drug interactions with agents metabolized by the cytochrome P-450 system. Consult with a pharmacist who can provide you with more information.

Mucositis

The incidence of mucositis with sorafenib and sunitinib varies but is potentially dose-limiting. With aggressive intervention you can help minimize significant sequelae. Functional mucositis is more common, especially with sunitinib, with patients complaining of symptomatic chang-

es in oral mucosa without clinically identifiable ulcerations or pseudo-membrane changes. Although an oral examination may demonstrate only mild erythema of mucosal surfaces, patients may complain of mouth pain, difficulty chewing coarse foods, and painful swallowing (dysphagia).

Some steps you can take:

- In some cases, IV hydration may be required.



FIGURE 1 Acral erythema and desquamation in a patient being treated with sunitinib. Occasionally observed with sorafenib therapy; typically less severe.



FIGURE 2 Hyperkeratosis (callus formation) in a patient being treated with sorafenib. Also seen with sorafenib therapy.



FIGURE 3 Subungual hemorrhage (splinter hemorrhage) seen with sunitinib, can also be seen with sorafenib. Not associated with pain or interference with function.

TABLE 3

Skin care products for hand-foot reactions

Skin care products	Product information
Cetaphil skin cleanser, Aveeno shower gel	Non-deodorant, non-fragrance products
Udderly Smooth, Gold Bond, Aveeno	Thicker products with more intense moisturizing properties than basic lotions. Anti-itch formulations are available.
Norwegian Formula: Soothing Relief Anti-Itch Moisturizer by Neutrogena	Contains dimethicone 1%, camphor 0.1%, and lidocaine
Norwegian Formula: Foot Cream by Neutrogena	Contains ceterayl alcohol, dimethicone, menthol, and urea
Bag Balm	May provide “cooling” effect from eucalyptus
Eucerin Cream	Best used at night due to greasy formulation
Eucerin Dry Skin Therapy	Contains trea and alpha hydroxy acid
Aquaphor Healing Ointment	Petrolatum 41%
Kerasal	Salicylic acid 5% exfoliates and softens skin; urea 10% moisturizes skin

- In addition, treatment interruption and symptomatic management, including narcotics for pain relief, should speed recovery with minimal weight loss.
- Consider modifying the dose to prevent recurrent severe mucositis in some patients. Ideally, earlier intervention and preventive strategies should allow patients to continue treatment at the initial dose.

Skin conditions

Dermatologic toxicities associated with sorafenib and sunitinib vary significantly in their type, time of onset, severity, duration, and response to therapeutic intervention. Reactions include dry skin, rash, pruritus, blistering, desquamation, and calluses. The appearance of rashes varies but typically consists of papules (circumscribed, solid elevations of skin without fluid) and macules (circumscribed < 1-cm areas of skin color change without elevation) or larger patches of macules. The onset of symptoms does not always recur following treatment and resolution of a particular dermatologic reaction. Symptoms may require treatment interruption or dose reduction but rarely require discon-

tinuation of therapy.

Acral erythema is associated with both sunitinib and sorafenib therapy, more commonly with the former. The relative appearance differs with each agent.

- It may occur on skin surfaces from repetitive friction, including plantar and palmar surfaces.
- It presents as symmetric erythematous areas on the palms and soles and may be preceded or accompanied by paresthesias.⁸
- These areas may be limited or widespread, can cause considerable pain, and may interfere with normal activities and ambulation.
- Desquamation of involved areas is more common with sunitinib than with sorafenib therapy (Figure 1).
- Areas of hyperkeratosis, especially on the soles, are more common with sorafenib therapy, resulting in the formation of thick calluses (Figure 2). Treatment of hyperkeratosis may include the use of topical exfoliating products such as Kerasal (available over the counter) or Keralac, a prescription drug. Instruct patients to apply these products only to calluses.

Subungual splinter hemorrhage is a unique side effect observed

in some patients receiving sorafenib or sunitinib therapy but does not require intervention or treatment modification (Figure 3).

- It forms within the epidermis of the nail bed and consists of a mass of blood in a layer of squamous cells that adhere to the undersurface of the nail.⁸
- These nail conditions are not associated with pain or change in nail integrity.

No treatment is required.

Dry skin generally is managed effectively with the use of gentle soap and the frequent application of moisturizing lotions. **Advise patients to:**

- To reduce the chance of skin reactions to chemicals, use soaps that contain no deodorant or fragrance.
- Use liquid shower gels instead of soap; it may be less irritating to the skin.
- Choose lotions with “anti-itch” formulations. (See Table 3 for a list of skin care products that can help.)

Pruritus may accompany dry skin or rash and can be disruptive during both waking and sleeping hours. **Advise patients to:**

- Apply more lotion to help reduce or eliminate pruritus on the trunk or extremities.
- Use lotions containing aloe vera or dimethicone.
- Use antidandruff shampoos and conditioners for scalp itch.
- Use hair care products containing tea tree oil, which may provide extra moisturizers and relief of symptoms.

Severe pruritus may require treatment interruption and/or a short course of methylprednisolone.

To manage rash:

- Change the type of soap used.
- Increase the application of lotions.
- Reduce friction from clothing.

More severe rashes may require treatment interruption, dose reduction, and possibly oral steroids.

Hair changes

Although total alopecia is not common with sorafenib or sunitinib,

Patient education resources

You can download copies of materials at these Web sites for your patients:

Sunitinib

- www.fda.gov/cder/drug/InfoSheets/patient/sunitinibPIS.htm
- www.sutent.com

Sorafenib

- www.fda.gov/cder/drug/InfoSheets/patient/sorafenibPIS.htm
- www.nexavar.com

CancerCare booklets

CancerCare, a national nonprofit organization, provides free, professional support services for anyone affected by cancer. The organization publishes a number of attractive booklets written for patients in easy-to-understand language. All the booklets are vetted by physicians and nurses.

You can download the booklets at the URLs listed below, or contact CancerCare for information on ordering bulk paper copies at publications@cancerca.org. A new booklet on dealing with rash and other skin reactions to targeted treatments will be available soon, as will an updated version of the diarrhea booklet.

Fatigue

- http://cancerca.org/pdf/booklets/ccf_fatigue.pdf

Mucositis

- http://cancerca.org/pdf/booklets/ccf_mouth_pain.pdf

Diarrhea

- http://cancerca.org/pdf/booklets/ccf_diarrhea.pdf
- http://chemocare.com/managing/diarrhea_and_chemotherapy.asp

hair thinning may occur. Hair depigmentation is more commonly experienced by patients taking sunitinib, although the overall incidence is not known; based on the author's experience, depigmentation is usually mild or moderate and occurs in approximately 60% of patients. No data have been reported at this time.

For some patients, changes in their appearance can affect their self image and quality of life. It is perhaps the most visible symbol of their disease. Be prepared to listen to your patients' concerns and offer comfort. Often the changes they are experiencing are not permanent and can serve as reminders that the treatment, while causing side effects, is actively fighting their cancer.

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Conflicts of interest: Ms. Wood is on the Speakers Bureau for Bayer and Onyx Pharmaceuticals, and Pfizer Oncology.