CHAPTER 7

Managing Side Effects of Multikinase Inhibitors

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Managing Side Effects of Multikinase Inhibitors (Sorafenib, Sunitinib)

Multikinase inhibitors are orally active agents that inhibit multiple-receptor kinases, some of which are implicated in tumor cell signaling, proliferation, angiogenesis, and apoptosis, as well as metastatic progression of cancer.1,2 Two multikinase inhibitors are approved for use in solid tumors: sorafenib and sunitinib. Sunitinib targets multiple cell surface tyrosine kinases, including vascular endothelial growth factor (VEGF) receptors 1, 2, and 3; platelet-derived growth factor (PDGF) receptors α and β, stem-cell factor receptor (KIT), FMS-like tyrosine kinase 3 (FLT3), colony-stimulating factor receptor type 1 (CSF-1R), and the glial cell line-derived neurotrophic factor receptor (RET).2 Sorafenib has activity against VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-β, KIT, FLT-3, and RET, and also targets several RAF intracellular serine/threonine kinases.1 Because multikinase inhibitors block multiple-cell-activation pathways, they may prevent or overcome drug resistance.3

Current and Future Uses

Sunitinib is currently approved for treatment of2
- Advanced renal cell carcinoma (RCC)
- Gastrointestinal stromal tumor (GIST) in patients whose disease progresses on imatinib therapy or who are intolerant to imatinib
  - For both indications, the recommended dosage is 50 mg PO once daily, with or without food, on a schedule consisting of 4 weeks on treatment and then 2 weeks off
    - Dose reductions or increases in increments of 12.5 mg are recommended based on individual patient tolerability

Sorafenib is indicated for the treatment of patients with1
- Advanced RCC
- Unresectable hepatocellular carcinoma (HCC)
  - The recommended dosage for both of the above indications is 400 mg (two 200-mg tablets) PO twice daily, taken without food at least 1 hour before or 2 hours after eating1
    - Sorafenib should be taken until the patient is no longer clinically benefitting from therapy, or until unacceptable toxicities occur1
    - If dosage reductions are needed to manage suspected adverse effects, the first reduction should be to 400 once daily.1 If an additional reduction is needed, 400 mg can be taken every other day1

More than 220 clinical trials are in progress investigating the efficacy of sunitinib in the treatment of a variety of cancers, including prostate cancer, breast cancer, glioblastoma, ovarian and fallopian-tube cancer, peritoneal cancer, and as adjuvant therapy for RCC. Nonmalignant conditions under study include neurofibromatosis. More than 240 trials are also recruiting or under way for sorafenib, for
tumors that include squamous cell carcinoma of the head and neck, pancreatic cancer, and non-small-cell lung cancer.

**Side Effects**

Common side effects associated with sorafenib include\(^1\):

- Fatigue
- Weight loss
- Rash/desquamation
- Hand-foot skin reaction (HFSR)
- Alopecia
- Diarrhea
- Anorexia
- Nausea
- Abdominal pain
- Hypophosphatemia (potentially severe)

Common side effects associated with sunitinib include\(^2\):

- Fatigue
- Asthenia
- Diarrhea
- Nausea
- Mucositis/stomatitis
- Vomiting
- Dyspepsia
- Abdominal pain
- Constipation
- Hypertension
- Rash
- Hand-foot syndrome
- Skin and hair discoloration
- Altered taste
- Anorexia
- Bleeding
Potentially severe or serious side effects of sorafenib and sunitinib include\(^1,2\)

- Cutaneous effects
- Hypertension
- Cardiac toxicity
- Hemorrhage
- Adrenal insufficiency/adrenal hemorrhage\(^a\)
- Hypothyroidism\(^a\)
- Gastrointestinal perforation\(^b\)
- Wound-healing complications\(^b\)

\(^a\)Associated with sunitinib.
\(^b\)Associated with sorafenib.

Side effects are graded on a scale of 1 to 4 according to the National Cancer Institute's Common Terminology Criteria for Adverse Events.

**Managing Selected Side Effects**

**Cutaneous Side Effects**

Providers should be aware of cutaneous side effects associated with multikinase inhibitor therapy. In one study of sorafenib, more than 90% of patients exhibited dermatologic changes associated with therapy.\(^4\) Cutaneous side effects of multikinase inhibitors may include HFSR, alopecia, dry skin, hair and skin discolorations, and subungual splinter hemorrhage.\(^5\)

**HFSR.** As with single kinase inhibitors, patients taking multikinase inhibitors have reported hand-foot reactions characterized by erythema, pallor, blistering, and desquamation,\(^6\) and often accompanied by paresthesia (tingling or intolerance to touch or heat).\(^5\) However, multikinase inhibitors also appear to be associated with the unique dose-dependent development of painful hyperkeratosis (Figure 1), which does not develop in the classic hand-foot syndrome.\(^5,7\) Painful hyperkeratotic areas on pressure points, surrounded by rings of erythematous and edematous lesions, are classically observed,\(^6\) and bullous lesions may be seen.\(^5\) The combination of hand-foot reactions and hyperkeratosis is characterized as HFSR.
HFSR develops in an estimated 30% to 60% of patients receiving sorafenib and 15% to 20% of patients treated with sunitinib. It appears 2 to 4 weeks following initiation of treatment and rapidly disappears if treatment is discontinued. Although HFSR is usually not a life-threatening side effect, it can significantly affect quality of life and be complicated by infection, pain, and limitation of daily activities. Sole involvement can result in walking impairment. Pre-existent sole hyperkeratosis can predispose to painful sole involvement and disability. Patients with pre-existing plantar hyperkeratosis may benefit from a pedicure before treatment is started.

There are three grades of HFSR, categorized according to severity of signs and symptoms and the impact on patient functioning (Figure 2). The following recommendations have been made with regard to managing HFSR in patients taking sorafenib:

- **Grade 1**: characterized by numbness, tingling, dysesthesia, paresthesia, painless swelling, and erythema or discomfort of the hands or feet. Symptoms are not considered to be disruptive to normal activities
  - Consider topical therapy

- **Grade 2**: characterized by painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities. Grade 3 is characterized by moist desquamation, ulceration, blistering or severe pain of the hands and feet, or severe discomfort that prevents patient from working or performing activities of daily living
  - For grade 2, consider topical therapy and other recommendations as for grade 1

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*Figure 1. HFSR. Keratotic Plantar Lesion is Surrounded by an Inflammatory Halo in a Patient Treated With Sunitinib.*

With permission from Robert C, Escudier B. Available at: http://www.cancernetwork.com/display-cme/article/10165/58823?pageNumber=2.
If no response to topical therapy within 1 week, two to three occurrences of grade 2 toxicity, or first or second occurrence of grade 3 toxicity, then
- Reduce dose by 50% or interrupt treatment until symptoms return to grade 0 or 1 (1–2 weeks is suggested) and then resume at 50% of the dose or dosing frequency. Full-dose treatment should be resumed after 3 to 4 weeks.
  - Treatment resumption is not always associated with the same side effects.
- If four occurrences at grade 2 or three at grade 3, discontinue sorafenib.

Comparable guidelines for managing HFSR in patients treated with sunitinib are not available. Sunitinib may have to be interrupted or decreased. When dosage reductions are required, sunitinib is generally reduced in increments of 12.5 mg.

It is important for providers to be aware of the association between multikinase inhibitors and HFSR to ensure proper referral and treatment. A thorough assessment of the patient’s hands and feet should be made before the patient begins a multikinase inhibitor. Early detection and intervention can prevent HFSR progressing to the point where potentially life-prolonging treatments must be withdrawn. To prevent and treat HFSR, providers should recommend treatments to inhibit hyperhidrosis (excessive sweating), if present, and should advise patients taking multikinase inhibitors to
- Avoid standing for long periods
- Use “shock absorbers” or gel inserts to relieve painful pressure points
- Use soft shoes (sandals may be helpful for some patients)
- Use cotton socks
- Avoid extremes of temperature, friction, or pressure on the skin
- Utilize the following symptomatic treatments as needed
  - Cooling of the affected area (which also promotes vasoconstriction, thereby possibly reducing drug exposure and related future toxicity in the local area)
  - Magnesium sulfate (Epsom salt) or aloe vera lotion
Over-the-counter emollients/keratolytics (containing salicyclic acid or urea)\(^5,7\)
- Topical petrolatum-lanolin ointment with antiseptic hydroxyquinolone to help maintain skin integrity\(^7\)

**Skin discoloration.** About 30% of patients treated with sunitinib develop yellowish skin coloration, possibly because sunitinib is bright yellow.\(^5\) Discoloration may be more noticeable in fair-skinned patients.\(^5\) Although less common, yellow skin discoloration has also recently been observed with sorafenib.\(^8\) As treatment continues, color intensification may be seen at the skin level, but the sclera and mucous membranes are spared (Figure 3).\(^8\) Transient intense yellow discoloration of urine, associated with excretion of the drug, has also been reported with sunitinib.\(^8,9\) Its intensity may parallel the intensity of the skin coloration.\(^8,9\) The discoloration is reversible within a few weeks following drug discontinuation.\(^8\)

**Figure 3. A: Diffuse Yellow Discoloration Resulting from the Use of Sorafenib. B and C: Associated Erythema and Desquamation of the Palms and Soles**\(^8\)

![Figure 3](image)


Providers should be aware of the possibility of skin discoloration with sunitinib and sorafenib to avoid unnecessary diagnostic tests. Other conditions that may resemble skin discoloration with multikinase inhibitors are carotenemia (which may be seen after ingestion of more than 30 mg of beta carotene daily), jaundice (which is also associated with discoloration of the sclera and urine), hypothyroidism, and cobalamin deficiency.\(^8\)

**Other skin reactions.** Sunitinib and sorafenib are associated with a number of other cutaneous side effects, most of which are easily managed.
- Subungual splinter hemorrhages\(^5\)
These hemorrhages may appear in up to two-thirds of patients on multikinase inhibitors. They are more common under the fingernails than the toenails.

- They appear as black or red lines that resemble wood splinters under the nail.
- Subungual splinter hemorrhages are moved forward with nail growth and can be scraped away when they reach the free margin of the nail.
- Subungual splinter hemorrhages are asymptomatic and do not require therapeutic management.

### Skin Dryness
- This is a frequent complaint of patients treated with sorafenib and sunitinib, affecting 20% to 30% of individuals.
- It can be treated with a skin emollient or body oil.

### Erythematous Rash
- About half of patients taking sorafenib develop an erythematous and squamous rash on the scalp and face that resembles seborrheic dermatitis.
- The rash generally emerges 1 to 2 weeks after the start of treatment, involving the mediofacial area and scalp skin. It is frequently preceded by or associated with scalp dysesthesia.
- The rash generally fades or disappears several weeks after beginning sorafenib treatment; therefore, treatment is usually unnecessary.
- For patients who request therapy, a short course of a topical emollient, 2% ketoconazole, or short course of topical steroids is appropriate.

### Hair Changes
- Sorafenib treatment can cause hair to become more brittle, finer, and curly. Darkening of the color may be reported.
- Mild diffuse alopecia may occur with both sorafenib and sunitinib.
  - Spontaneous regrowth generally occurs with continuing therapy. Often, the new hair is curlier than the patient's hair prior to starting sorafenib.
- Sunitinib frequently causes hair depigmentation after 5 to 6 weeks of treatment. Periods off and on therapy may result in “bands” of depigmented and normally pigmented hair.
  - This is reversible after 2 to 3 weeks of treatment.

### Periocular Edema
- Sometimes seen in patients receiving sunitinib. While the exact cause is unknown, it may be due to the effects of this agent on interstitial fluid homeostasis.
- Periorbital edema generally does not require treatment.
Hypertension

Hypertension is a commonly reported side effect of therapy in patients taking either of the multikinase inhibitors. In the HCC population, hypertension was reported in 9.4% of patients treated with sorafenib compared with 4.3% of patients treated with placebo. Treatment-emergent hypertension was reported in 16.9% of patients taking sorafenib in the phase 3 clinical trial of advanced RCC versus 1.8% taking placebo. Hypertension was usually mild to moderate, occurred early in the course of treatment, and was managed with standard antihypertensive therapy. However, a systematic review of 3567 patients who received single-agent sorafenib at a starting dose of 400 mg twice daily in clinical trials showed a substantially higher incidence of all-grade hypertension (23.4%) than reported previously, with a 5.7% incidence of high-grade hypertension. Those taking sorafenib had a six-fold increased risk of developing hypertension compared with controls.

With sunitinib, hypertension was observed in 30% of patients being treated for advanced RCC; grade 3 hypertension was reported in 10%. In the treatment of GIST, the overall incidence of hypertension with sunitinib was similar to placebo, although the incidence of grade 3 hypertension was 4% versus 0 with placebo.

The increased risk of hypertension with multikinase inhibitors might be related to their activity against the VEGF receptor. The resulting impairments in angiogenesis may cause a decrease in the density of microvessels, endothelial dysfunction leading to decreased nitric oxide production and increased oxidative stress, and alterations in neurohormonal factors or the renin-angiotensin-aldosterone system.

A pre-eclampsia-like syndrome characterized by hypertension and proteinuria has also been seen after starting therapy with both sorafenib and sunitinib. The development of this syndrome was described in a series of seven patients by Patel et al. Patients were identified through the development of edema, hypertension, proteinuria, or hypoalbuminemia. The mean time between starting therapy and developing hypertension was 27 weeks. All seven patients developed proteinuria, with peak urine protein excretion occurring at a median of 24 weeks.

Specific recommendations for the prevention and treatment of hypertension in patients taking multikinase inhibitors include

- Advise patients to make healthy lifestyle choices, including regular exercise, weight control, moderate alcohol consumption, and sodium restriction (<2 g/day).
- Instruct patients to self-monitor their blood pressure and give them systolic and diastolic threshold numbers to use as a trigger for notifying healthcare professionals for early assessment and intervention
- Have patients keep a diary of blood pressure measurements to help them adhere to treatment and communicate better with the healthcare team.
• Monitor blood pressure weekly during the first 6 weeks of multikinase inhibitor therapy. After 6 weeks, monitor blood pressure and treat if necessary in accordance with standard medical practice\textsuperscript{1,10}

• Treat hypertension with standard antihypertensive therapy,\textsuperscript{1,2} particularly beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, or other calcium channel blockers, such as amiodipine and nifedipine\textsuperscript{10}
  o Nondihydropyridine calcium channel blockers, such as diltiazem and verapamil, should be avoided as they are inhibitors of P450 CYP3A4 and may increase concentrations of sunitinib and sorafenib\textsuperscript{10}
  o Consider effects of antihypertensive agents on angiogenesis. Nifedipine may promote VEGF secretion, whereas enalapril and candesartan can inhibit VEGF-related angiogenesis\textsuperscript{10}

• Consider treatment with phosphodiesterase inhibitors or nitrate derivatives, which can increase nitric oxide levels\textsuperscript{10}

• Temporarily or permanently suspend multikinase inhibitor therapy for patients with severe hypertension (>200 mm Hg systolic or >110 mm Hg diastolic) or hypertension that persists despite antihypertensive therapy\textsuperscript{1,2,10}

**Hemorrhage**

Bleeding ranging from mild epistaxis (nosebleed) to severe hemorrhages have been observed in patients taking multikinase inhibitor therapy.

In the clinical trials of sunitinib in RCC, 30% of patients taking this agent experienced a bleeding event, compared with 8% receiving interferon alfa.\textsuperscript{2} Eighteen percent of sunitinib patients in the GIST trial had a bleeding episode, but so did 17% of patients in the placebo group.\textsuperscript{2} Epistaxis was the most common bleeding occurrence in these studies; other events included rectal, gingival, upper gastrointestinal, genital, and wound bleeding.\textsuperscript{2}

The incidence of hemorrhage in the phase III clinical study of sorafenib in RCC was 15% in those receiving sorafenib versus 8% in placebo patients. One patient in each group died as a result of hemorrhage.\textsuperscript{1} Conversely, in the trial using sorafenib in HCC, hemorrhage/bleeding was reported in 18% of patients receiving sorafenib and 20% of patients who received placebo.\textsuperscript{1}

Tumor-related hemorrhage has been observed in patients taking sunitinib.\textsuperscript{2} These bleeding events may have sudden onset, and in the case of pulmonary tumors, may present as severe and life-threatening pulmonary hemorrhages or hemoptysis.\textsuperscript{2} (Sunitinib is not approved in the treatment of lung tumors.) In addition, rare and sometimes fatal gastrointestinal complications, including gastrointestinal perforation, have occurred in patients with intra-abdominal malignancies.\textsuperscript{2}

Intracerebral hemorrhage (ICH) is emerging as a particular concern with both sunitinib and sorafenib therapy. The presence of brain metastases appears to increase ICH risk. Poussel and Culline\textsuperscript{13} reported
on a series of 67 patients with metastatic RCC who were treated with sorafenib, 400 mg twice daily, or sunitinib, 50 mg daily, in 6-week cycles (4 weeks of treatment followed by 2 weeks off treatment). Four of seven patients who had brain metastases at the start of treatment developed acute, massive, fatal ICH within 2 to 14 days after starting multikinase inhibitor therapy. Given the high incidence of ICH in this series among patients with brain metastases, the authors considered brain metastases “a major risk factor” for ICH in those taking sorafenib or sunitinib.

- In general, multikinase inhibitor therapy should be permanently discontinued in any patient who requires medical intervention for a bleeding event.2
- Educate the patient about management of minor bleeding and the importance of reporting any bleeding events
  - If epistaxis occurs, instruct the patient to lean forward and pinch the bridge of the nose between the thumb and forefinger
  - If epistaxis lasts for >10 to 15 minutes, or is accompanied by faintness or dizziness, instruct the patient to call his or her healthcare provider

**Cardiac Toxicity**

Cardiac toxicities are potentially life-threatening side effects associated with multikinase inhibitors. In the clinical trials of sunitinib in advanced RCC, more patients treated with sunitinib experienced a decline in left ventricular ejection fraction (LVEF) compared with those receiving interferon alfa or placebo.2 In patients with GIST, 11% of sunitinib patients had treatment-emergent LVEF values below normal limits.2 Nine patients with LVEF changes recovered without intervention, while another five recovered following intervention consisting of dose reduction, or the addition of antihypertensive or diuretic medications.2 Sunitinib also prolongs the QT interval in a dose-dependent manner, which may lead to an increased risk for ventricular arrhythmias, including Torsade de pointes. Torsade de pointes has been observed in <0.1% of patients taking sunitinib.2

The incidence of cardiac toxicities with sunitinib may be higher than indicated from the clinical trials. Patients with cardiac events within 12 months prior to use of sunitinib were excluded from clinical studies; therefore, it remains unknown whether patients with concomitant cardiac conditions may be at increased risk for the development of drug-related left ventricular dysfunction. A recent study of 36 patients treated with sunitinib at the approved dose found that 8% developed clinically significant symptomatic heart failure, with 19% experiencing a decline of at least 15% in left ventricular function.14

The information on cardiac toxicities with sorafenib is more sparse; however, treatment-emergent cardiac ischemia and infarction have both been reported.3 Among patients with RCC, the incidence of cardiac ischemia/infarction was 2.9% in the sorafenib group versus 0.4% in the placebo group. Patients with unstable coronary artery disease or recent myocardial infarction were excluded from the study. In patients with HCC, 2.7% of sorafenib-treated patients developed cardiac ischemia/infarction versus 1.3% of the placebo group.1
The following are specific recommendations for the treatment of cardiac toxicities in patients taking sunitinib:

- In those with pre-existing cardiac disease, providers should weigh the benefits of sunitinib against the potential for developing clinical signs and symptoms of left ventricular dysfunction\(^2\)
  - Patients with cardiac conditions should be evaluated at baseline for left ventricular dysfunction, and monitored throughout the course of treatment
- Consider a baseline evaluation of ejection fraction in those without cardiac risk factors\(^2\)
- Sunitinib should be used with caution in patients with a history of prolonged QT interval, those taking antiarrhythmics, or those with pre-existing cardiac disease, bradycardia, or electrolyte disturbances. Periodic monitoring with electrocardiograms and measurement of electrolyte levels (magnesium and potassium) should be considered\(^2\)
- In patients with clinical manifestations of congestive heart failure during treatment, therapy should be discontinued\(^2\)

In patients with no clinical evidence of congestive heart failure but an ejection fraction of <50% and 20% below baseline, the dose should be reduced and/or interrupted\(^2\)

Specific recommendations for the management of cardiac toxicities in patients taking sorafenib include:

- Instruct patients to get emergency help and immediately report any chest pain, shortness of breath, lightheadedness, fainting, nausea, vomiting, or excessive sweating\(^1\)
- Consider temporary or permanent discontinuation of sorafenib in patients who develop cardiac ischemia and/or infarction\(^1\)

**Additional Side Effects**

- Adrenal insufficiency/adrenal hemorrhage
  - Adrenal hemorrhage has been observed in animal studies of sunitinib. Clinical studies have reported rare abnormalities, including decreased peak cortisol levels following stimulation, but no patients have been found to have clinical evidence of adrenal insufficiency\(^2\)
    - Monitor adrenal function in patients under stress (eg, surgery, trauma, severe infection)\(^2\)
- Hypothyroidism
  - Treatment-emergent hypothyroidism has emerged in 3% to 4% of patients treated with sunitinib in clinical trials\(^1\)
    - Measure baseline thyroid function\(^2\)
    - Monitor all patients taking sunitinib for signs and symptoms of hypothyroidism. Perform laboratory measurements to assess thyroid function in any patients with signs or symptoms suggestive of hypothyroidism\(^2\)
    - Treat hypothyroidism in accordance with standard medical practice\(^2\)
- Wound-healing complications have been reported in patients taking sorafenib\(^1\)
Sorafenib should be temporarily interrupted in patients undergoing major surgical procedures. Timing of treatment resumption is at the physician’s discretion and based on adequate wound healing.

Drugs Interactions

Sunitinib
Sunitinib is a substrate of cytochrome P450 (CYP 450) 3A4. As such, its plasma levels are affected by other drugs that are inhibitors or inducers of this enzyme.

Strong inhibitors of the P450 3A4 enzyme may increase sunitinib plasma concentrations. For example, concomitant administration of sunitinib with ketoconazole resulted in a 49% increase in the maximum plasma concentration of sunitinib and its primary active metabolites. Selection of an alternative concomitant medication with no or minimal CYP3A4 inhibition is recommended.

CYP3A4 inducers may decrease sunitinib plasma concentrations. For example, concomitant administration of sunitinib with rifampin resulted in a 23% decrease in the maximum plasma concentration of sunitinib and its primary active metabolites. Selection of an alternative concomitant medication with no or minimal CYP3A4 induction is recommended. A dose increase in sunitinib may be considered if coadministered with CYP3A4 inducers, including rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, and phenobarbital. Please refer to the Appendix for a list of other common CYP3A4 inducers and inhibitors.

Sorafenib
Sorafenib is metabolized by the liver, undergoing oxidative metabolism mediated by CYP3A4 and glucuronidation mediated by UGT1A9. Inducers of CYP3A4 (eg, rifampin, St John’s wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone) may decrease exposure to sorafenib, and inhibitors of CYP3A4 theoretically could increase exposure to sorafenib. However, concomitant administration of sorafenib with the potent CYP3A4 inhibitor ketoconazole did not alter the metabolism of sorafenib. Sorafenib is a competitive inhibitor of CYP2C19, CYP2D6, and CYP3A4; however, it has been deemed unlikely to alter the metabolism of substrates of these enzymes. In fact, sorafenib has not been shown to inhibit metabolism of warfarin (a CYP2C9 substrate). Sorafenib also inhibits CYP2B6 and CYP2C8, so sorafenib may interfere with metabolism of substrates of these enzymes. In vitro testing suggests that sorafenib does not induce CYP1A2 or CYP3A4. Refer to the Appendix for lists of common substrates, inhibitors, and inducers of CYP450 enzymes.

Sorafenib also inhibits glucuronidation by UGT1A1 and UGT1A9. Caution is recommended when administering sorafenib with compounds metabolized or eliminated primarily by the UGT1A1 pathway (eg, irinotecan), which can result in increased exposure to these compounds.
Concomitant administration of sorafenib with doxorubicin resulted in a 21% increase in total systemic exposure to doxorubicin. Coadministration of sorafenib and docetaxel increased docetaxel area under the curve (AUC) by 36% to 80%, and increased maximum docetaxel concentration by 16% to 32%. Fluorourcil AUC has been both increased (21%–47%) and decreased (10%) when administered with sorafenib. Therefore, caution is indicated when sorafenib is given concurrently with any of these medications. Sorafenib has no effect on pharmacokinetics of gemcitabine, oxaliplatin, or paclitaxel.  

### Special Populations

#### Sunitinib

Sunitinib is a pregnancy category D medication (ie, there is evidence of fetal risk, but benefits outweigh risks). Given that angiogenesis is a critical component of embryonic and fetal development, inhibition of angiogenesis associated with sunitinib may result in adverse effects on pregnancy. If sunitinib is used during pregnancy, or if the patient becomes pregnant while receiving this drug, she should be apprised of the potential hazard to the fetus. Women of childbearing potential should be counseled to avoid pregnancy while receiving treatment with sunitinib. It is not known whether sunitinib is excreted in human breast milk, and given the potential for serious adverse reactions in nursing infants, the patient should decide whether to discontinue nursing or to stop sunitinib.  

No overall differences in safety have been reported with sunitinib in patients aged 65 years or older compared with younger patients. Sunitinib has not been studied in pediatric patients. In addition, no change in treatment is indicated in the presence of hepatic impairment.  

#### Sorafenib

As with sunitinib, sorafenib is considered a pregnancy category D medication. Patients should be advised to avoid becoming pregnant while on sorafenib. Adequate birth control should be used by both the patient and partner while taking sorafenib and for at least 2 weeks after stopping therapy. It is not known whether sorafenib is excreted in human breast milk, and given the potential for serious adverse reactions in nursing infants, the patient should decide whether to discontinue nursing or to stop sorafenib.  

No changes in treatment with sorafenib are recommended based on age, gender, or body weight. Mean sorafenib AUC is 30% lower in Asians than in Whites. Patients with mild or moderate (Child-Pugh A or B) hepatic impairment may have sorafenib AUCs that are 23% to 65% lower than in patients with normal hepatic function. No dosage adjustment is necessary for renal impairment, but sorafenib has not been studied in dialysis patients.
References


