

Clinical Pharmacology: Concise Drug Reviews

Sorafenib and Sunitinib

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Enumerate the clinical indications for sorafenib and sunitinib therapy.
2. Describe the mechanism of action and the pharmacokinetics of sorafenib and sunitinib.
3. Analyze the toxicity profile and appraise the therapeutic effects associated with sorafenib and sunitinib.

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INTRODUCTION

Sorafenib (Nexavar®; Bayer Pharmaceuticals, West Haven, CT) (Fig. 1A) and sunitinib (Sutent®; Pfizer Inc., New York, NY) (Fig. 1B) are orally bioavailable, small molecule inhibitors of multiple intracellular and receptor protein kinases that are components of signaling pathways that control tumor growth and angiogenesis. These agents have similar drug profiles and overlapping targets, which are summarized in Table 1. Sorafenib and sunitinib are currently approved by the U.S. Food and Drug Administration for advanced renal cell cancer (RCC) in adults [1]. Sorafenib is also approved for unresectable hepatocellular carcinoma (HCC) [2] and sunitinib is approved for gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate [3]. These differing clinical indications are likely a result of the different development plans of the respective drug companies, rather

than the specific mechanism for each drug. There are currently studies underway for GIST patients with sorafenib and for HCC patients with sunitinib.

CLINICAL USE

Sorafenib is available as 200-mg tablets, and the recommended dose for adults is 400 mg twice daily (BID) on a continuous dosing schedule, administered at least 1 hour before or 2 hours after food intake. Sorafenib should be held or the dose should be reduced to 400 mg once daily or every other day for management of intolerable, sorafenib-related toxicities [4]. In phase I studies combining sorafenib with carboplatin plus paclitaxel and gemcitabine, full-dose sorafenib (400 mg BID) was tolerable when combined with standard doses of these chemotherapeutic agents [5].

Sunitinib is available as oral capsules of 12.5, 25, and 50

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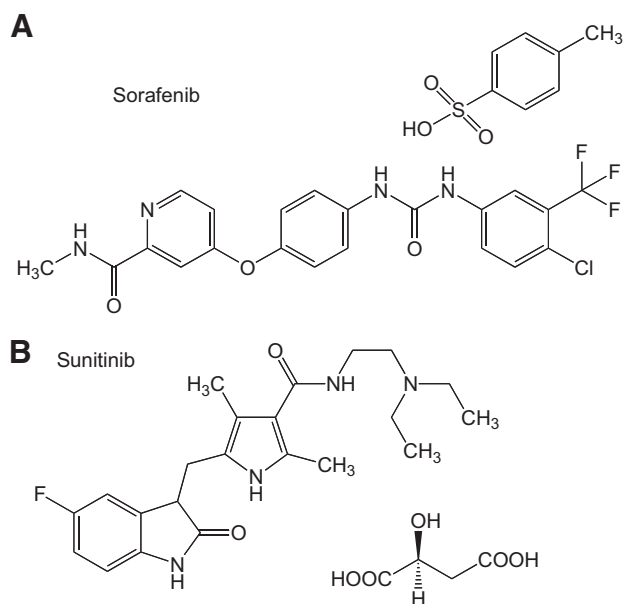


Figure 1. Chemical structures. **(A):** Chemical structure of sorafenib. **(B):** Chemical structure of sunitinib.

mg. The recommended dose is 50 mg once daily for 4 weeks followed by a 2-week rest. Dosage reductions in 12.5 mg increments are recommended for intolerable sunitinib-related toxicities [6].

MECHANISM OF ACTION

The regulation of cellular processes, including most of those involved in oncogenesis, such as cell proliferation and apoptosis, is biochemically mediated through reversible phosphorylation of specific signaling proteins [7]. Phosphorylation is typically an activation step that propagates a signal through a hierarchal signaling cascade by sequential phosphorylation of signaling proteins, which may also be protein kinases.

Dysregulation of these signaling pathways in tumors plays a critical role in the pathogenesis and maintenance of the malignant phenotype in most cancers. Some examples are chromosomal translocations that result in tumor-specific biologically active fusion proteins (e.g., Bcr-Abl), gain- or loss-of-function mutations, and amplification of the genes that encode signaling proteins with kinase activity. As a result, these aberrant receptor or intracellular protein kinases are potential targets for new cancer therapies.

Sorafenib and sunitinib are potent inhibitors of multiple protein kinase targets involved in tumor cell proliferation and angiogenesis. Sorafenib was initially identified as an inhibitor of Raf serine/threonine kinase isoforms, which are in the Ras signaling pathway. The in vitro screening assay included the mutated oncogenic form of B-Raf [8].

Sunitinib was identified in biochemical kinase screening assays as a potent inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, and VEGFR-3, which are involved in angiogenesis, and platelet-derived growth factor receptors (PDGFRs) [9]. Sorafenib also inhibits VEGFRs and PDGFR- β , and both drugs inhibit the c-Kit, Flt-3, and RET receptors, which are mutated and constitutively active in GIST, acute myelogenous leukemia, and thyroid tumors, respectively [3, 8, 9].

PHARMACOKINETICS

Bioanalysis

Sorafenib and sunitinib are quantified in plasma using high-performance liquid chromatography with tandem mass spectrometry detection [10, 11].

Absorption

At the recommended sorafenib dose of 400 mg orally BID, the maximum plasma concentration (C_{max}) after the first dose was in the range of 2.3–3.0 $\mu\text{g/ml}$ and the time to achieve maximum concentration was variable and in the range of 1.0–12.3 hours. Substantial accumulation of sorafenib was observed with continuous dosing, and steady-state concentrations were reached after 7 days [12].

Plasma concentrations of sorafenib after oral administration were highly variable across patients and did not increase in proportion to the dose as it was escalated in phase 1 trials [12]. The area under the curve (AUC), which is a measure of drug exposure, increased marginally when the dose was escalated beyond 400 mg BID [13]. A high-fat meal reduced sorafenib bioavailability by 29% [5], thus the label recommends that sorafenib be taken without food.

After a single 50-mg dose of oral sunitinib, the mean C_{max} was 28 ng/ml, reached at a median of 5 hours after the dose [10]. Trough plasma concentrations of sunitinib and its major active metabolite SU12662 increased in proportion to the dose in a dose-finding study [10]. Sunitinib accumulates three- to fourfold and SU12662 accumulates seven- to tenfold during continuous administration, and steady-state concentrations of both compounds were reached by 10–14 days. The bioavailability of sunitinib or SU12662 was not significantly altered by food taken prior to drug administration in healthy volunteers [6].

Protein Binding

Sorafenib and sunitinib are highly protein bound. In in vitro studies with human plasma, sorafenib is 99.5% bound and sunitinib and its primary active metabolite are 95% and 90% bound, respectively [4, 6]. Therefore, free (nonpro-

**TABLE 1. SUMMARY TABLE**

| | | |
|-------------------------|---|--|
| Generic name | Sorafenib | Sunitinib malate |
| Commercial name | Nexavar® | Sutent® |
| Molecular weight | 464.8 g/mole | 532.6 g/mole |
| Mechanism of action | Inhibition of CRAF, BRAF, VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- β , RET, Flt3, c-Kit | Inhibition of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- α , PDGFR- β , RET, Flt3, c-Kit, CSF-1R |
| Route of administration | Oral | Oral |
| | Reduced by fatty foods 29% | Unaffected by food |
| Protein binding | 99.5% | 95% |
| Metabolism | Metabolized primarily by oxidative metabolism mediated by CYP3A4 as well as glucuronidation mediated by UGT1A9 | Metabolized by CYP3A4 to primary active metabolite SU12662, which accounts for 23%–37% of total exposure; SU12662 is further metabolized by CYP3A4 |
| Elimination | 77% feces (50% as parent drug) and 19% urine (as glucuronidated metabolites) | Predominantly feces (61%), urine (16%) |
| Terminal half-life | 25–48 hours | 40–60 hours |
| Main toxicities | Rash, diarrhea, hand–foot syndrome, fatigue, hypertension | Fatigue, diarrhea, nausea, hypertension, hand–foot syndrome |
| Main drug interactions | UGT1A1 and UGT1A9 substrates, docetaxel, doxorubicin, fluorouracil, CYP2B6 and CYP2C8 substrates, CYP3A4 inducers | CYP3A4 inhibitors such as ketoconazole and CYP3A4 inducers such as rifampin |

Abbreviations: CSF, colony-stimulating factor; CYP, cytochrome P450; PDGFR, platelet-derived growth factor receptor; UGT, uridine diphosphate glucuronosyl transferase; VEGFR, vascular endothelial growth factor receptor.

tein-bound) drug concentrations of sunitinib are tenfold higher than those of sorafenib at the same total plasma concentration.

Metabolism and Elimination

Sorafenib and sunitinib are eliminated primarily through hepatic metabolism and biliary excretion. Sorafenib undergoes oxidative metabolism by cytochrome P450 (CYP)3A4 primarily to an N-oxide metabolite, and is subsequently conjugated with glucuronide (15% of the dose). The conjugation step is catalyzed by uridine diphosphate glucuronosyl transferase 1A9. After oral administration of 100 mg of sorafenib, 77% was excreted in the feces (50% as parent drug) and 19% was excreted in the urine as glucuronide conjugates [4, 14]. Sorafenib has a relatively long elimination half-life ($t_{1/2}$) of 20–27 hours [12].

Sunitinib is also metabolized primarily via CYP3A4 to the active N-de-ethylated metabolite SU12662, which accounts for 23%–37% of the total exposure to active compounds. SU12662 undergoes a second N-de-ethylation step by CYP3A4 to the inactive metabolite SU14335, but this second N-de-ethylation occurs at a slower rate, which ac-

counts for the longer half-life of the active metabolite [15]. Both sunitinib and its metabolites are eliminated predominantly by biliary excretion into the feces (61%). Renal elimination accounts for 16% of the administered dose. Most of the drug in the feces and urine is parent drug [3]. Sunitinib had a long terminal $t_{1/2}$ in the range of 41–86 hours in a phase I study [10].

Drug Interactions

Although sorafenib and sunitinib are metabolized by CYP3A4, which can be inhibited or induced by a number of other drugs and environmental chemicals, biliary excretion of the unchanged parent drug accounts for more than half of the elimination of sorafenib and sunitinib, and this route of elimination is not affected by agents that inhibit CYP3A4 activity. A study examining concomitant administration of ketoconazole, a CYP3A4 inhibitor, with sorafenib in healthy male volunteers demonstrated no change in the pharmacokinetics of sorafenib [14]. In contrast, a study of single-dose sunitinib with ketoconazole in healthy male volunteers demonstrated a significant increase in the mean

C_{\max} (4.8 ± 1.1 versus 7.6 ± 1.6 ng/ml) and AUC (268 ± 95.4 versus 454 ± 119 ng·hr/ml) of sunitinib [16].

Potent CYP3A4 inducers may increase sorafenib metabolism, but no clinical studies have evaluated this potential interaction [1]. Concomitant rifampin, a potent CYP3A4 inducer, resulted in a fourfold lower sunitinib plasma exposure and 2.5-fold lower plasma C_{\max} when compared with sunitinib alone in healthy male volunteers [17]. However, SU12662 was 1.4-fold greater after CYP3A4 induction with rifampin, such that the combined exposure to sunitinib and SU12662 was 50% lower with rifampin [6, 17].

Sorafenib was given in phase I clinical trials in combination with carboplatin, dacarbazine, gemcitabine, oxaliplatin, and paclitaxel, with no detectable drug interactions observed [1]. However, the doxorubicin AUC was 47% greater when coadministered with sorafenib, although no significant difference in toxicity was observed despite the greater doxorubicin exposure [18]. When coadministered with irinotecan, exposure was greater for both irinotecan (26%–42%) and its active metabolite SN-38 (70%–120%), but diarrhea from irinotecan was not appreciably worse with the combination [19].

Alterations with Special Populations

Dose adjustments are not necessary for age for sorafenib and sunitinib in adults. Both drugs are predominantly metabolized in the liver, and previous studies suggest that dose adjustments are not indicated in patients with Child-Pugh Class A or B cirrhosis for either drug [4, 6]. New guidelines from a phase I study of sorafenib in patients with hepatic and renal dysfunction were recently published [20]. Cohorts of patients with mild to severe hepatic or renal dysfunction were evaluated. Patients with moderate to severe hepatic and renal dysfunction did not tolerate the 400-mg BID dose that is recommended for patients with normal organ function. Thus, the following starting dose guidelines for sorafenib were recommended:

- Patients with a bilirubin level exceeding the upper limit of normal (ULN) but $\leq 1.5 \times$ ULN or an aspartate aminotransferase (AST) level $>ULN$ or creatinine clearance (CrCl) of 40–59 ml/minute should receive 400 mg BID.
- Patients with a bilirubin level of $1.5\text{--}3 \times$ ULN and any AST level or a CrCl of 20–39 ml/minute should receive 200 mg BID.
- Patients with a bilirubin level of $3\text{--}10 \times$ ULN and any AST level do not tolerate 200 mg every third day.
- Patients with an albumin level <2.5 mg/dl and any bilirubin and AST level should receive 200 mg once daily.

- A safe dose has not been defined for patients with a CrCl <20 ml/minute.
- Patients on hemodialysis (with any CrCl) should receive 200 mg once daily.

Clinicians should consider dose escalation in an individual patient if the drug is well tolerated [20].

The safety and efficacy of sorafenib and sunitinib in pediatric patients are currently being studied. Both agents cause reversible bone abnormalities in growing, but not aged, animal models [4, 6]. This is a potentially unique toxicity that has not been previously described in adult trials but would be of particular interest in children.

PHARMACODYNAMICS

Although sorafenib was originally developed as a Raf inhibitor to block signaling pathways involved in tumor proliferation, the drug's antitumor effect also draws from its antiangiogenic properties and its inhibitory effect on other protein kinases. As with other multitargeted agents, the primary protein kinase target or targets responsible for the therapeutic effect may be tumor specific.

The effects of sorafenib and sunitinib on their multiple targets have been monitored in patients treated in clinical trials. Increases in serum VEGF have been noted in patients treated with sorafenib in phase II and III trials [21]. Levels of c-Kit, hepatocyte growth factor, and soluble VEGFR-2 and VEGFR-3 were significantly reduced in patients with HCC treated with sorafenib [2]. Sunitinib significantly reduced the levels of phosphorylated PDGFR- β in tumor biopsies of patients with GIST, for whom treatment with sunitinib resulted in clinical benefit. It also inhibited VEGFR and angiogenesis in patients with GIST, RCC, or other advanced malignancies [3].

THERAPEUTIC EFFECTS

For patients with advanced RCC, the median progression free survival (PFS) time was 5.5 months for patients treated with sorafenib, compared with 2.8 months for those treated with placebo ($p < .01$) [22]. Partial responses were reported in 10% of patients treated with sorafenib [22]. In a randomized phase III trial of sorafenib compared with placebo for patients with unresectable HCC, sorafenib demonstrated a statistically significant overall survival benefit (median, 10.7 months for sorafenib versus 7.9 months for placebo; $p < .01$) [23].

In a randomized phase III trial in patients with progressive metastatic or unresectable GIST, patients treated with sunitinib had a significantly longer time to tumor pro-

Table 2. Skin toxicity grading scale

| Grade | Skin toxicity | Occurrence | Suggested modification |
|-------|--|--|---|
| 1 | Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema, or discomfort of the hands or feet that does not disrupt the patient's normal activities | Any occurrence | Continue treatment with sorafenib and consider topical therapy for symptomatic relief |
| 2 | Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities | First occurrence | Continue treatment with sorafenib and consider topical therapy for symptomatic relief; if no improvement within 7 days, see below |
| | | No improvement within 7 days or second or third occurrence | Interrupt sorafenib treatment until toxicity resolves to grade 0-1; when resuming treatment, decrease dose by one dose level (400 mg daily or 400 mg every other day) |
| | | Fourth occurrence | Discontinue treatment |
| 3 | Moist desquamation, ulceration, blistering, or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living | First or second occurrence | Interrupt sorafenib treatment until toxicity resolves to grade 0-1; when resuming treatment, decrease dose by one dose level (400 mg daily or 400 mg every other day) |
| | | Third occurrence | Discontinue treatment |

From Nexavar® (sorafenib) [package insert]. West Haven, CT: Bayer Healthcare, 2005.

gression (TTP) than those receiving placebo (median TTP, 27.3 weeks versus 6.4 weeks; $p < .01$) [24]. In a phase III randomized study comparing sunitinib with interferon (IFN)- α in patients with treatment-naïve metastatic RCC, an interim analysis demonstrated a significantly longer PFS time in patients treated with sunitinib (median PFS, 47.3 weeks versus 22 weeks). In addition, patients treated with sunitinib had an objective response rate of 27.5%, compared with 5.3% for those treated with IFN- α [6].

TOXICITY

Chronic administration of sorafenib and sunitinib is associated with manageable, mild-to-moderate toxicities. The most common sorafenib toxicities in prior clinical trials were reversible skin rash, hand-foot syndrome, diarrhea, anorexia, alopecia, abdominal pain, fatigue, and hypertension [4, 12]. Rash and hand-foot syndrome were dose dependent, with increasing severity and frequency with higher doses [1]. Some common laboratory abnormalities observed were hypophosphatemia, asymptomatic elevated lipase, and mild hematologic abnormalities (lymphopenia, neutropenia, and thrombocytopenia, typically grade ≤ 2) [4].

The most common toxicities reported for sunitinib in

clinical trials were fatigue, diarrhea, nausea, stomatitis, rash, hand-foot syndrome, and hypertension. The most frequently noted laboratory abnormalities for patients in RCC trials were asymptomatic elevated lipase. Of note, the left ventricular ejection fraction decreased in 15% of patients enrolled in two consecutive phase II advanced RCC trials of sunitinib [1].

PATIENT INSTRUCTIONS AND RECOMMENDATIONS FOR SUPPORTIVE CARE

Sorafenib should be swallowed whole, without food. The manufacturer has recommended dose modifications for skin toxicity based on a unique grading scale developed specifically for sorafenib (Table 2) [4].

Sunitinib may be taken with or without food. The manufacturer recommends monitoring for clinical signs and symptoms of heart failure by measuring baseline and periodic left ventricular ejection fractions in all patients receiving sunitinib [1]. Hypothyroidism has been reported with sunitinib, and patients should have baseline thyroid function tests and be clinically monitored for signs and symptoms of hypothyroidism [6].

Both drugs should not be taken while pregnant, and men and women should use effective birth control while

taking sorafenib or sunitinib because both may be teratogenic [4, 6].

Hypertension is a common adverse reaction to both drugs. The relative risk for developing any grade hypertension compared with controls with sorafenib is 6.1, and with sunitinib it is 3.9 [25]. Therefore, blood pressures should be monitored frequently. The manufacturers of sorafenib recommend weekly monitoring for the first 6 weeks and thereafter in accordance with standard medical practice [4, 6]. Patients who experience mild to moderate hypertension should be treated with standard antihypertensive therapy and continue treatment. In cases of severe or persistent hypertension, despite institution of antihypertensive therapy, temporary or permanent discontinuation of sorafenib or sunitinib should be considered [4, 6, 25].

Clinicians should obtain baseline and serial CBCs, chemistries including phosphate and liver function tests,

and pancreatic enzymes. Physical examinations with blood pressure monitoring should be performed regularly, and adverse events should be treated symptomatically and with dose modifications as needed.

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AUTHOR CONTRIBUTIONS

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Trabectedin

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In the August 2009 print issue of *The Oncologist*, Mace Rothenberg was erroneously listed as a section editor for the article “Trabectedin.” Dr. Rothenberg no longer serves as editor of the Clinical Pharmacology section and was not involved in the development or the review of this article.

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