

Sunitinib

An oral chemotherapeutic agent

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There are a projected 51,190 new cases of RCC and 12,890 deaths due to RCC in the United States in 2007.² As many as 30% of patients who present with renal-cell carcinoma are diagnosed with metastatic disease. Renal cell carcinoma is highly resistant to chemotherapy and only a subset of patients benefit from cytokine therapy with high-dose interleukin 2 and/or interferon- α . Anywhere from 5-20% of patients respond to treatment and median overall survival is around 12 months.^{3,4} Gastrointestinal stromal tumor is a soft-tissue sarcoma with an estimated 4,500 to 6,000 new cases in the United States each year.⁵ Imatinib has remained the first line treatment for GIST; however, most patients will develop resistance and there are no effective options for therapy for patients after failure on imatinib.⁶

PHARMACOLOGY/PHARMACOKINETICS

Sunitinib (Sutent[®], Pfizer) inhibits multiple receptor tyrosine kinases, including platelet-derived growth factor receptors (PDGFR α and PDGFR β) and all of the isoforms of vascular endothelial growth factor receptors (VEGFR1, VEGFR2, and VEGFR3). The stem cell factor receptor (KIT) is also inhibited by sunitinib, along with colony-stimulating factor receptor Type 1 (CSF-1R), Fms-like tyrosine kinase-3 (FLT3), and the glial cell-line derived neurotrophic factor receptor (RET).^{1,2} Receptor tyrosine kinases are fundamental for tumor growth and survival, as they are responsible for a variety of cellular responses, such as differentiation, proliferation, migration, invasion, angiogenesis, apoptotic signaling, and cell survival.² Gain-of-function KIT gene mutations are connected with 85-90% of GISTs while 5% of GISTs are associated with PDGFR α .⁶ These mutations result in the activation of KIT and PDGFR α , which are the main reasons for the development of the malignant phenotype and the continuation of disease in most GIST tumors.⁸

The median steady-state trough plasma concentration (C_{\min}) of sunitinib and its active metabolite in all patients taking the recommended dose in one multicenter phase II trial was 84.3 ng/mL, which is within the range of 50 to 100 ng/mL shown to inhibit target receptor tyrosine kinases in preclinical models.⁷

Following oral administration of sunitinib, the median steady-state peak plasma concentration (C_{\max}) occurs between six and 12 hours; food has no effect on its bioavailability.¹ The extent of plasma protein binding of sunitinib and its primary active metabolite is 95% and 90%, respectively, and the apparent volume of distribution (V_d/F) is 2230 L. Steady-state is reached after 10

Summary

Indications. Sunitinib (Sutent[®], Pfizer) is approved for the treatment of gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate and for the treatment of advanced renal cell carcinoma (RCC).¹

Monitoring Parameters. CBC, cardiac function (LVEF, ECG) in patients with a cardiac history or symptoms of CHF, BP, thyroid function.

Dose. The recommended dose of sunitinib is 50 mg orally once daily for four weeks on treatment followed by two weeks off treatment. Dose adjustments of 12.5 mg/day are recommended based on individual safety and tolerability.

Pediatrics. The safety and efficacy of sunitinib in pediatric patients have not been studied in clinical trials.

Geriatrics. In clinical trial subjects 65 years of age and over, no overall differences in safety or effectiveness were observed between younger and older patients.

Renal Insufficiency. No data available.

Hepatic Insufficiency. No dose adjustment is required in patients with Child-Pugh Class A or B hepatic impairment. Sunitinib was not studied in subjects with severe (Child-Pugh Class C) hepatic impairment.

Pregnancy Category. Category D

Breast Feeding. It is not known whether sunitinib or its primary active metabolite is excreted in human milk. Sunitinib and its metabolites are excreted in rat milk.

Cost. The cost for 28 capsules (one course of therapy) is \$1,829.99 for the 12.5 mg capsules (\$65.36/capsule), \$3,759.90 for the 25 mg capsules (\$134.28/capsule), and \$7,249.74 for the 50 mg capsules (\$258.92/capsule). The daily cost of treatment for a patient taking the 50 mg capsules at the recommended dose of 50 mg daily for four weeks followed by two weeks off treatment (42 days total) is \$172.61.

to 14 days of daily dosing and total oral clearance ranges from 34 to 62 L/hr. Sixteen percent of the dose of sunitinib is renally eliminated while the major route of elimination is in the feces (61%). The elimination half-lives of sunitinib and its primary active metabolite were found to be 40-60 hours and 80-110 hours, respectively, after a 50 mg oral dose was given to healthy volunteers. Sunitinib is largely metabolized by the microsomal enzyme CYP3A4 to generate its primary active metabolite, which accounts for 23% to 37% of the total exposure.

Patients with impaired renal function were not included in the clinical studies of sunitinib.¹ The studies excluded patients who had a serum creatinine greater than two times the upper limit of normal. Patients who had hepatic impairment (Child-Pugh Class A or Child-Pugh Class B) experienced comparable systemic exposure to those with normal hepatic function.¹ Patients with Child-Pugh Class C hepatic impairment did not receive sunitinib and clinical studies excluded patients with ALT or AST levels greater than two and a half times the upper limit of normal



or greater than five times the upper limit of normal if due to liver metastases.

CLINICAL TRIALS

Advanced Renal Cell Carcinoma

Motzer et al evaluated the efficacy and safety of sunitinib in a multicenter phase II trial of 63 patients with MRCC who had experienced failure of one cytokine (interleukin-2 or interferon- α)-based therapy or who experienced intolerable toxicity.⁷ Eligible patients also had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate organ function (hepatic, renal, cardiac, hematologic); patients were excluded if they had evidence of brain metastases or if they had suffered a noteworthy cardiac event within 12 months of the beginning of the study. The primary end point was objective tumor response rate (complete or partial response, as defined by Response Evaluation Criteria in Solid Tumors (RECIST)). Time to progression and safety were secondary end points.

Patients received sunitinib 50 mg orally daily with or without meals for four weeks and then had no therapy for two weeks. This six-week cycle was repeated until disease progression, unacceptable toxicity, or withdrawal of consent. The dose of sunitinib could be increased in increments of 12.5 mg per day (maximum: 75 mg per day) if there were no treatment toxicities. The dose of sunitinib could be decreased for grade three to four toxicity to a minimum of 25 mg per day, based on a nomogram. Computed tomography (CT) and/or magnetic resonance imaging (MRI) were used with RECIST and bone scans to assess efficacy. This was performed after the first two cycles, the fourth cycle, and after every two cycles from then on until treatment end to assess objective clinical response. The Functional Assessment of Chronic Illness Therapy-Fatigue scale (FACIT-Fatigue) and the EuroQoL EQ-5D instrument (EQ-5D) were conducted to assess quality of life. The FACIT-Fatigue scale is a 13-item questionnaire that assesses self-reported tiredness, weakness, and difficulty conducting usual activities due to fatigue.⁸ The EQ-5D instrument is a generic (disease non-specific) quality of life (QoL) instrument which has patients rate their health status and allows comparisons between different patient groups and the general population.⁹

Twenty-five patients had a partial response (40%; 95% CI, 28% to 53%), 17 patients (27%) achieved stable disease ≥ 3 months, and 21 patients (33%) experienced either progressive disease or stable disease of < 3 months or were not able to be assessed. Median time to progression was 8.7 months (95% CI, 5.5 to 10.7) and median survival was 16.4 months (95% CI, 10.8 to not yet attained). Patients were treated for a median of 9 months (range, < 1 to 24+ months). At the time of data analysis, eight patients of the 25 patients who were partial responders were receiving therapy and were progression-free for 21 to 24 months after the start of therapy. The median and mean scores of the EQ-5D questionnaires did not change significantly from baseline through 24 weeks of treatment. The same was true of the FACIT-Fatigue questionnaire scores. Patients' fatigue level trended higher during the treatment period; scores came back to baseline during the two weeks off treatment.

The adverse effect profile of sunitinib was evaluated. The National Cancer Institute Common Toxicity Criteria version 2.0 was used to assess the severity of adverse events. The most common adverse effects were lymphopenia (72%; 32% grade 3), neutropenia (45%; 11% grade 3), fatigue (38%; 11% grade 3), anemia (37%; 8% grade 3), hyperlipasemia (24%; 19% grade 3), and diarrhea (24%; 3% grade 3). A decrease in left ventricular ejection fraction (LVEF) was the reason that four patients were discontinued from the study: only one patient had clinical signs and symptoms with dyspnea. Twenty-two patients (35%) received a dose reduction from 50 to 37.5 mg per day and two of these patients required an additional dose reduction to 25 mg per day. The most frequent causes for reducing the dose were asymptomatic increases in either serum lipase or amylase (11 patients) and fatigue (five patients).

This study shows that sunitinib has activity in MRCC after therapy fails with a cytokine, but this study is limited because it is open-label, single-arm, and response was only assessed by the investigators.

Motzer et al performed an open-label, single-arm, multicenter phase II trial of 106 patients in order to verify the efficacy of sunitinib in MRCC patients who experienced disease progression on cytokine therapy.⁴ Eligibility and exclusion criteria were the same as the prior study with the only difference being that eligible patients were required to have clear-cell renal cell carcinoma and have undergone a nephrectomy. The primary objective was to evaluate the objective response rate (complete or partial response). The secondary objectives were to determine the progression-free survival, overall survival, duration of response, and safety of sunitinib.

Sunitinib was given as a 50-mg dose orally once daily for four weeks followed by two weeks off therapy. This six-week cycle of treatment was continued until patients withdrew consent, until there was evidence of the progression of disease, or until the patient experienced intolerable toxicity. The dose could be reduced to 37.5 mg per day and then to 25 mg per day for toxicity. Clinical response was evaluated with the use of CT and/or MRI and bone scans by using RECIST after each of the first four cycles and after every other cycle from then on.

The median age of the patients was 56 years with the most common site for metastases being the lungs (81%). One patient was removed from the study after a subsequent biopsy revealed a diagnosis other than clear-cell renal cell carcinoma. According to the independent third-party assessment, a partial response was seen in 36 patients (34%; 95% CI, 25% to 44%) and 30 patients (29%) had stable disease for three months or more. Of the 36 responders identified by independent third-party review of response, ten patients had progressed or died at the time of data analysis and because of this, the data for median duration of response were not yet available. Fifty-six patients (53%) experienced progression of disease or death on the study and 8.3 months (95% CI, 7.8 to 14.5 months) was the median progression-free survival as reported by the independent assessment. The six-month survival was 79% (95% CI, 70% to 86%) and median overall survival had not yet been reached.

An analysis of the two phase II trials by Motzer et al. was per-

formed with the 168 evaluable patients. This analysis revealed that, based on the assessment of the investigators, 71 (42%) responded to treatment, 40 (24%) had stable disease lasting three months or longer, and 57 (34%) had stable disease lasting less than three months, experienced disease progression, or were not evaluable. Median progression-free survival was 8.2 months (95% CI, 7.8 to 10.4 months). Median progression-free survival in responders was 14.8 months (95% CI, 10.9 to 24.2 months). Of these 168 patients, 163 (97%) had a prior nephrectomy, 82 (49%) had prior interferon-alfa therapy, 68 (40%) had prior interleukin-2 therapy, and 18 (11%) had prior interferon-alfa plus interleukin-2 treatment. The most common site of metastases was the lung (82%) and 93 patients (55%) had three or more disease sites. A prognostic factor analysis for survival revealed that lower hemoglobin values were a predictor of shorter progression-free survival (≥ 13 g/dL vs. < 13 g/dL for males and ≥ 11.5 g/dL vs. < 11.5 g/dL for females; $p < 0.001$).

The safety and adverse effect profile of sunitinib was also assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. The median number of completed treatment cycles was five (range, 0-11 cycles), with diarrhea and fatigue being the most common adverse events (20% and 28%, respectively). The only grade 4 adverse events were laboratory abnormalities: neutropenia (2%), increased lipase (3%) and anemia (2%). Overall, 42% of patients experienced neutropenia, 28% had increased lipase, 26% had anemia and 21% experienced thrombocytopenia. Hypertension (16%), dyspepsia (16%), hand-foot syndrome (15%), nausea (13%), stomatitis (13%), anorexia (12%) and mucosal inflammation (12%) were other common adverse events. Eight patients (4.7%) were found to have a decrease in LVEF, but no patients had clinical signs or symptoms of congestive heart failure. Sunitinib was discontinued in 12 patients (11%) due to adverse events, but these events were not specified. There was one patient who died during the study due to a myocardial infarction, which was thought possibly to be related to sunitinib treatment.

This study confirms the activity of sunitinib in MRCC after therapy fails with a cytokine, but this study is also limited because it is an open-label, single-arm trial.

Motzer et al evaluated sunitinib versus interferon alfa as first-line treatment of MRCC in an international, randomized, multicenter, phase III trial.³ The trial enrolled 750 patients with clear-cell MRCC who were 18 years of age or older and had not been treated with systemic therapy. Patients received either repeated six-week cycles of sunitinib ($n=375$) (50 mg once per day for four weeks and then two weeks off treatment) or interferon alfa ($n=375$) (three million units subcutaneously three times weekly for one week, six million units subcutaneously three times weekly for the second week, and nine million units subcutaneously three times weekly for the remainder of treatment).³ Eligible patients also had an ECOG performance status of 0 or 1, measurable disease and adequate organ function (hematologic, renal, cardiac, hepatic, and coagulation). Patients were excluded for the presence of metastases to the brain, as were patients with uncontrolled hypertension or those who had experienced a cardiac event or cardiac disease within the 12 months prior to the study.

Dose reductions were permitted for patients experiencing adverse events, based on a nomogram per protocol. Sunitinib could be reduced in increments of 12.5 mg per day to a minimum dose of 25 mg daily and interferon alfa could be reduced in increments of three million units to a minimum dose of three million units three times weekly.

Treatment cycles were repeated until unacceptable toxicity was reported, progression of disease occurred or the patient withdrew consent. Progression-free survival was the primary end point of the study with secondary end points of overall survival, objective response rate and safety. RECIST was used to evaluate response by using CT and/or MRI at baseline, at the end of treatment for cycles one through four and then every two cycles until treatment end. The Functional Assessment of Cancer Therapy – General (FACT-G) and FACT-Kidney Symptom Index (FKSI) questionnaires were conducted to evaluate health-related quality of life. The FACT-G questionnaire is a general quality of life instrument intended for use with a variety of chronic illness conditions and the FKSI questionnaire is a kidney cancer-specific version of the Functional Assessment of Cancer Therapy (FACT) questionnaire which evaluates specific disease-related symptoms.¹⁰

The median treatment duration was six months in the sunitinib group and four months in the interferon alfa group. There were 248 patients (66%) in the sunitinib group and 126 patients (34%) in the interferon alfa group receiving ongoing treatment at the time of analysis. Treatment was most often discontinued either due to disease progression (25% of patients in the sunitinib group and 45% of patients in the interferon alfa group, $p < 0.001$) or adverse events (8% in the sunitinib arm and 13% in the interferon alfa arm, $p=0.05$). Withdrawal of consent (1% in the sunitinib group and 8% in the interferon alfa group, $p < 0.001$) and protocol violation ($< 1\%$ in each group) were other reasons for discontinuing treatment. The median progression-free survival was 11 months in the sunitinib patients (95% CI, 10 to 12) compared to five months in the interferon alfa patients (95% CI, 4 to 6). This produces a hazard ratio of 0.42 (95% CI, 0.32 to 0.54; $p < 0.001$). Median overall survival was not yet available for either group in this analysis, but 13% of patients who had received sunitinib had died, as had 17% of patients who had received interferon alfa. At the time of analysis, this comparison did not meet the study's baseline criteria for level of significance. Objective response rate was 31% in the sunitinib group (95% CI, 26 to 36) and 6% in the interferon alfa group (95% CI, 4 to 9) ($p < 0.001$), with imaging studies for 88 patients not included in the independent third-party review because they had not been evaluated yet. Stable disease was seen in 48% of the sunitinib patients and 49% of the interferon patients. There were 72 patients (21%) in the sunitinib group who had progressive disease or could not be evaluated compared to 147 patients (45%) of the interferon alfa group. There was a significant difference in the patient reports of health-related quality of life according to the FACT-G and FKSI questionnaires, with the sunitinib group reporting better scores than the interferon alfa group ($p < 0.001$).

A dose interruption due to adverse events was required in 38% of sunitinib patients and in 32% of the interferon alfa patients while a dose reduction was required in 32% and 21%

of patients, respectively. The adverse events that necessitated interruption, reduction or discontinuation of treatment were not specified. Adverse events were assessed using the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 3.0. Rates of toxicities for sunitinib versus interferon alfa included neutropenia (72% vs. 46%, respectively), thrombocytopenia (65% vs. 21%), hyperamylasemia (32% vs. 28%), diarrhea (53% vs. 12%), hypertension (24% vs. 1%), hand-foot syndrome (20% vs. 1%), lymphopenia (60% vs. 63%), decline in ejection fraction (10% vs. 3%), mucosal inflammation (20% vs. 1%), skin discoloration (16% vs. no cases), rash (19% vs. 6%) and fatigue (51% vs. 51%). The rate of grade 3 or 4 fatigue was reported significantly more in the interferon alfa group (12%) than in the sunitinib group (7%) ($p < 0.05$). The rates of grade 3 or 4 neutropenia, leukopenia, hyperamylasemia, hyperlipasemia and thrombocytopenia occurred significantly more often in the sunitinib group than in the interferon alfa group ($p < 0.05$). The sunitinib group had significantly higher rates than the interferon alfa group in grade three vomiting (4% vs. 1%) ($p < 0.05$), hypertension (8% vs. 1%) ($p < 0.05$), hand-foot syndrome (5% vs. no cases) ($p < 0.05$) and diarrhea (5% vs. no cases) ($p < 0.05$). Significantly more chills, fever, myalgia and influenza-like symptoms were experienced by the interferon alfa patients.

An update of this trial was presented at the Annual Meeting of the American Society of Clinical Oncology (ASCO) in June 2007.¹¹ The median duration of treatment was 11 months (range 1 to 25) for sunitinib compared to four months (range 1 to 22) for interferon alfa. The overall response rate was reported only for the investigator assessment and was 44% (95% CI, 39 to 49) for sunitinib and 11% (95% CI, 8 to 15) for interferon alfa ($p < 0.000001$), which included four complete responses with sunitinib and two with interferon alfa. The median progression-free survival was 11 months (95% CI, 10 to 11) for sunitinib compared to four months (95% CI, 4 to 5) for interferon alfa. The median duration of response was 12 months in the sunitinib group ($n=165$) (95% CI, 10 to 14) and 10 months in the interferon alfa group ($n=43$) (95% CI, 8 to 17).

This study reveals that sunitinib has efficacy as first-line treatment for MRCC. Long-term survival and efficacy data are needed for further evaluation.

Gastrointestinal Stromal Tumor

Demetri et al studied the safety and efficacy of sunitinib in patients with advanced GIST who developed resistance to or were intolerant of imatinib therapy in a randomized, double-blind, placebo-controlled, parallel-group, multicenter, international, phase III trial.⁶ The primary efficacy measure was time to tumor progression, which was assessed by a third-party imaging laboratory. Comparison of progression-free survival, duration of response, overall survival and objective response rate were secondary objectives. Eligibility criteria included: measurable disease, GIST that did not respond to radiation, surgery or other combination therapy with intent to cure, and failure or intolerance of prior therapy with imatinib. The last dose of imatinib had to be two or more weeks prior to randomization and all toxicities due to imatinib or other prior therapies had to be reduced to a grade

of one or less. Patients had an ECOG performance status of 0 or 1, satisfactory cardiac, renal, and hepatic function, a hemoglobin level of 9.0 g/dL or greater, absolute neutrophil count of 1500 per mcL or greater and a platelet count of 100,000 per mcL or more.

There were 312 patients randomized (2:1) to therapy with sunitinib ($n=207$) or placebo ($n=105$), with all patients receiving best supportive care. The regimen included one dose orally daily for four weeks followed by two weeks of no treatment; the dose of sunitinib was begun at 50 mg orally daily. Patients who were found to have progressive disease during the study (according to RECIST) were allowed to continue receiving sunitinib if on active treatment previously and those who had been on placebo were allowed to cross over and be given open-label sunitinib. The dose of sunitinib was reduced in 12.5 mg per day increments if patients experienced grade three or four adverse effects, according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Efficacy was measured with RECIST using CT, spiral CT, and/or MRI performed by a blinded independent third-party radiology lab. Disease status was evaluated at baseline, at the end of four weeks of each treatment cycle and at treatment end.

At the time of the prespecified interim analysis, after 149 patients had disease progression (defined by RECIST) or death, sunitinib had a statistically significant advantage over placebo in time to tumor progression and progression-free survival. The intent-to-treat (ITT) median time to tumor progression was 27.3 weeks (95% CI, 16 to 32.1) for sunitinib and 6.4 weeks for placebo (95% CI, 4.4 to 10) (HR 0.33; 95% CI, 0.23 to 0.47; $p < 0.0001$). Progression free survival was 24.1 weeks (95% CI, 11.1 to 28.3) for sunitinib and 6 weeks (95% CI, 4.4 to 9.9) for placebo (HR 0.33; 95% CI, 0.24 to 0.47; $p < 0.0001$), while median time to tumor response was 10.4 weeks for patients on sunitinib (95% CI, 9.7 to 16.1 weeks). The study was then unblinded and patients were given the option to switch to open-label sunitinib treatment. The median number of treatment cycles was two (range, zero to nine) at the time the data collection was discontinued; 134 patients (65%) taking sunitinib and 34 patients (32%) taking placebo were still taking double-blinded treatment while 19 patients (9%) in the sunitinib group and 59 patients (56%) in the placebo group had crossed over to receive open-label sunitinib therapy after disease progression. Treatment was withdrawn for 72 patients (35%) taking sunitinib and for 71 patients (68%) taking placebo, with progression of disease being the most reported cause of discontinuation (71% and 92% of patients discontinuing, respectively). Twenty-three patients (11%) receiving sunitinib required a dose reduction and 57 patients (28%) required an interruption in dosing, compared to 0% and 20% for placebo, respectively.

The effect of any baseline factors on treatment was evaluated and all subgroups were found to have a HR less than 0.5, showing that sunitinib was more beneficial than placebo for all analyzed subgroups. Overall survival data were not mature at the time. The objective response rate for the ITT patients included 14 patients (7%) in the sunitinib group who showed a partial response and no patients showed a partial response in the placebo

group (95% CI, 3.7 to 11.1%; $p=0.006$). Stable disease was seen in 120 (58%) sunitinib patients and in 50 (48%) placebo patients. Progressive disease was found in 39 (19%) patients in the sunitinib group and in 39 (37%) patients in the placebo group. Of the 59 placebo patients who crossed over to treatment with sunitinib, six showed a partial response.

Adverse events were evaluated at the time of efficacy analysis in 168 (83%) patients who received sunitinib and in 60 (59%) patients who received placebo. There were no reports of decrease in LVEF, pancreatitis or congestive heart failure. Grade one or two fatigue (29% vs. 20% for sunitinib and placebo, respectively), diarrhea (26% vs. 8%), skin discoloration (25% vs. 6%), nausea (23% vs. 10%), anorexia (19% vs. 5%), dysgeusia (18% vs. 2%), stomatitis (15% vs. 2%), vomiting (15% vs. 5%), hand-foot syndrome (9% vs. 2%), mucosal inflammation (12% vs. 0%) and dyspepsia (11% vs. 0%) were all more common in the sunitinib group than the placebo group. Patients in the sunitinib group also experienced more grade one or two leukopenia (52% vs. 5%), neutropenia (43% vs. 4%), lymphopenia (40% vs. 30%) and thrombocytopenia (36% vs. 4%). The most common grade three events in the sunitinib patients were fatigue (5%), diarrhea (3%), hand-foot syndrome (4%), neutropenia (8%), lymphopenia (9%), anemia (4%), leukopenia (4%) and thrombocytopenia (4%).

Sunitinib displayed efficacy in this study in increasing the time to tumor progression in patients with GIST and is a therapeutic option for increasing progression-free survival after failure of imatinib therapy, but showed little benefit in tumor response.

DRUG INTERACTIONS

In vitro studies indicate that sunitinib does not induce or inhibit major CYP enzymes.¹ Sunitinib is a major substrate of the microsomal enzyme CYP3A4 and therefore, drug-drug interactions occur with substrates that affect this enzyme. Concurrent administration of a single dose of sunitinib with ketoconazole, a strong CYP3A4 inhibitor, in healthy volunteers resulted in 49% and 51% increases in the combined sunitinib plus primary active metabolite C_{max} and $AUC_{0-\infty}$ values, respectively.¹ Other strong CYP3A4 inhibitors that could potentially increase sunitinib concentrations include itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole and grapefruit juice. Concurrent administration of a single dose of sunitinib with rifampin, a strong CYP3A4 inducer, in healthy volunteers resulted in a 23% and 46% reduction in the combined sunitinib plus primary active metabolite C_{max} and $AUC_{0-\infty}$ values, respectively.¹ Other strong CYP3A4 inducers that could potentially decrease sunitinib concentrations include dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital and St. John's Wort. A dose reduction for sunitinib to a minimum of 37.5 mg daily should be considered when it is administered with strong CYP3A4 inhibitors and a dose increase for sunitinib to a maximum of 87.5 mg daily should be considered when it is administered with strong CYP3A4 inducers.¹

MEDICATION SAFETY

There may be a concern regarding sunitinib as a possible look-

alike and sound-alike medication with sorafenib. Care should be exercised in storage and dispensing of these agents to avoid confusion and errors.

ADVERSE EFFECTS

A clearer picture of the adverse events associated with sunitinib may be seen with the phase III trial comparing sunitinib with placebo in patients with GIST.⁶ Grade three or four toxicity occurred more often in the sunitinib group than with placebo (56% vs. 51%). Grade three or four toxicities that were reported more often with the sunitinib group than with placebo were diarrhea (4% vs. 0%), hypertension (4% vs. 0%), rash (1% vs. 0%), hand-foot syndrome (4% vs. 3%), asthenia (5% vs. 3%), fatigue (5% vs. 2%) and stomatitis (1% vs. 0%).^{1,6} Laboratory abnormalities that were more common in the sunitinib group than in the placebo group were neutropenia (53% vs. 4%), lymphopenia (38% vs. 16%), anemia (26% vs. 22%), thrombocytopenia (38% vs. 4%), increased AST/ALT (39% vs. 23%), increased lipase (25% vs. 17%), increased alkaline phosphatase (24% vs. 21%), increased amylase (17% vs. 12%), elevated total bilirubin (16% vs. 8%), decreased LVEF (11% vs. 3%), increased serum creatinine (12% vs. 7%), hypokalemia (12% vs. 4%) and hypernatremia (10% vs. 4%).^{1,6} Eight patients (4%) in the sunitinib group developed hypothyroidism, including one grade four case. The most common grade three or four laboratory abnormalities in the sunitinib group included neutropenia (10%), increased lipase (10%), increased amylase (5%) and thrombocytopenia (5%).^{1,6}

Decreased LVEF has been reported with sunitinib treatment. Twenty-five patients (15%) experienced a decrease in LVEF to below the lower limit of normal in the two single-arm trials of MRCC.⁵ In the sunitinib versus interferon alfa trial in MRCC, 78/375 (21%) patients in the sunitinib group experienced a LVEF value below the lower limit of normal, as did 44/360 (12%) patients in the interferon alfa group. Decreases in the LVEF of >20% from baseline and to below 50% were reported in 13 patients taking sunitinib (4%) and in four patients taking interferon alfa (1%) in the same study.¹ In patients without clinical evidence of congestive heart failure, but who have a LVEF of <50% and >20% below baseline, the dose of sunitinib should be reduced and/or interrupted. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) was seen in 4% of GIST patients being treated with sunitinib, 1% of GIST patients receiving placebo, 5% of MRCC patients who were treatment-naïve being treated with sunitinib and in 1% of MRCC patients who were treatment-naïve being treated with interferon alfa. Hemorrhagic events have also been reported in patients receiving sunitinib. In the trial of sunitinib versus interferon alfa for MRCC, 30% of sunitinib patients experienced a bleeding event compared to 8% of patients who received interferon alfa. In the GIST study, 18% of sunitinib patients and 17% of the placebo patients experienced a bleeding event, with epistaxis being the most frequent event. Diarrhea and fatigue were the most frequently reported adverse events in the two single arm studies in MRCC.^{4,7}

COST, DOSE AND HOW SUPPLIED

Sunitinib is provided as 12.5 mg, 25 mg, and 50 mg capsules. The recommended dose of sunitinib for GIST and advanced renal cell carcinoma is one 50 mg oral dose taken once daily for four weeks, followed by two weeks off treatment. Treatment costs are outlined in the table below.

DISCUSSION

Sunitinib has the advantage of being an oral chemotherapeutic agent that allows patients to be treated on an ambulatory basis. However, oral anti-cancer agents bring with them unique reimbursement challenges. Sunitinib is expensive and may not be covered by a patient's prescription insurance. Reimbursement from third-party payers can be complicated by required medica-

Capsule Strength	Cost per Course of Therapy n=28 capsules (4 weeks on/2 weeks off)	Daily Cost (4 weeks on/2 weeks off) (42 days total)	Cost per Capsule
12.5 mg	\$1,829.99	\$43.57	\$65.36
25 mg	\$3,759.90	\$89.52	\$134.28
50 mg	\$7,249.74	\$172.61	\$258.92

tion pre-authorization and off-label use restrictions, which are becoming increasingly common in oncology. One study reported that 68% of oncologists placed "high importance" on prescribing for off-label uses (suggesting that no substantial change in current off-label prescribing is likely in the future), but that 30% of oncologists said that they have decreased their prescribing for off-label indications due to the challenges associated with reimbursement.¹²

Some manufacturers of high-cost oral medications have turned to specialty pharmacies to supply their medications to patients. Sorafenib is another oral multikinase inhibitor similar to sunitinib, but unlike sunitinib, is only supplied by specialty pharmacy providers. In order for the patient to receive sorafenib from the specialty pharmacy, the prescribing oncologist is required to complete extensive enrollment forms. The applications for many of these oral oncology medications are similar to the applications used by patient assistance programs, requiring patients to disclose financial and other clinical information. This process is time-consuming and can delay the start of treatment for some patients.

Specialty pharmacies are becoming increasingly common as health insurers and employers strive to manage the extremely high cost of specialized medications.¹³ With their high volume, specialty pharmacies are able to leverage prices downward and offer insurers clinical programs that few traditional ambulatory pharmacies can offer (e.g., adherence and clinical outcome monitoring). However, specialty pharmacies fragment the medication management process (separating products they supply from those supplied by patients' local pharmacies). This fragmentation adds a degree of complexity to products that are already extremely complicated, expensive and potentially very risky.¹⁴ These medications often have numerous side effects and drug-drug interactions which a pharmacist would not be able to screen

for or counsel patients about when the specialty medication is not documented on the patient's local profile. In the hospital setting, medication-reconciliation activities may be threatened because specialty medication therapies are often not incorporated in the hospital's standard record-keeping system. There is also a liability risk related to the inability to guarantee the medication's integrity, especially when considering specialty injectable medications that patients receive from a specialty pharmacy and then bring into a hospital or clinic to be administered.¹⁴

As availability of specialty pharmacies increases, and policies requiring their use become more common, pharmacists will face new challenges and must begin taking special care to monitor cancer care for patients who must receive medications from specialty pharmacies.

CONCLUSION

Sunitinib is considered first-line treatment in patients with MRCC and is a therapeutic option to increase the progression-free survival in patients with GIST who have had disease progression on or failure of imatinib therapy. Sunitinib is well-tolerated and has the advantage

of being an oral agent that can be taken on an outpatient basis.

It is recommended that patients with a cardiac history or symptoms of CHF be monitored closely for decreases in cardiac function. ●

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