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Review Article

Scope of Sorafenib Tosylate in Renal Cell Carcinoma

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Abstract

Renal cell carcinoma is a kidney cancer that originates in the lining of the proximal convoluted tubule. It is the most common type of kidney cancer in adults, responsible for approximately 80% of cases. It is also known to be the most lethal of all the genitourinary tumors. Sorafenib received FDA regular approval on December 20, 2005 for the treatment of advanced RCC. Sorafenib belongs to the class of diaryl ethers. Sorafenib is a kinase inhibitor that decreases tumor cell proliferation in vitro. The long-term treatment with sorafenib is associated with continued efficacy and a well-tolerated safety profile. It can be used in combination with other antineoplastic drugs effectively. Based on its mechanism of action and findings in animals, sorafenib may cause fetal harm when administered to a pregnant woman. Greater sensitivity of some older individuals was observed. However, treatment with sorafenib prolongs progression-free survival in patients with advanced renal cell carcinoma in whom previous therapy has failed.

1. Introduction

Renal Cell Carcinoma (RCC), also known as hypernephroma is a kidney cancer that originates in the lining of the proximal convoluted tubule, the very small tubes in the kidney that filter the blood and remove waste products. RCC is the most common type of kidney cancer in adults, responsible for approximately 80% of cases. It is also known to be the most lethal of all the genitourinary tumors. It is most likely to spread to neighboring lymph nodes, the lungs, the liver, the bones, or the brain. The metastatic stage of renal cell carcinoma occurs when the disease invades and spreads to other organs. This presents a special challenge to oncologists, as about 70% of patients develop metastases during the course of their disease.

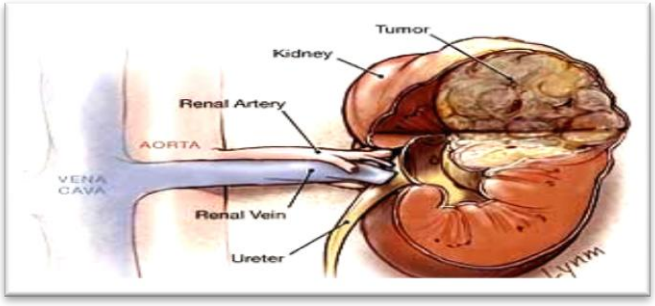

Figure 1: Renal cell carcinoma

***1.1 Epidemiology*:**

From 1975 to 2006, the incidence of kidney cancer rose 2% annually in the United States. The American Cancer Society estimated that by 2015 there would be much more than 57,760 cases (35,430 in males and 22,330 in females) of malignant tumors of the kidney diagnosed, with 12,890 deaths (8,160 in males and 4,820 in females). The incidence in men is greater than in women (1.6:1).Renal cell cancer accounted for 80% of this incidence and mortality. It is more common in people of Northern European ancestry (Scandinavians) and North Americans than in those of Asian or African descent.

1.2 Etiology

The main causative factors for RCC are Cigarette smoking, Obesity, Hypertension, Phenacetin-containing analgesics taken in large amounts.

1.3 Symptoms

The symptoms include - Abdominal pain, Back pain, Blood in the urine, Enlargement of the veins around a testicle (varicocele), Swelling or enlargement of the abdomen, and Unintentional weight loss.

2. Sorafenib tosylate

Chemically Sorafenib is 4-[4-[[4-chloro-3-(trifluoromethyl) phenyl]carbamoylamino] phenoxy] -*N*-methyl-pyridine-2-carboxamide. It is a new smaller molecule, multi-kinase inhibitor for the treatment of patients with advanced renal cell carcinoma (RCC). Sorafenib received FDA regular approval on December 20, 2005 for the treatment of advanced RCC. The phase III Treatment Approaches in Renal cancer Global Evaluation Trial (TARGET) indicated that sorafenib is effective and well tolerated in advanced renal cell carcinoma patients. The long-term treatment with sorafenib is associated with continued efficacy and a well-tolerated safety profile.

2.1 Characteristics

Sorafenib tosylate occurs as white to pale yellow colored, tasteless and odorless crystalline powder and is insoluble in water. Its molecular formula is $C_{21}H_{16}ClF_3N_4O_3$ and has a molecular weight of 464.825.

The recommended daily dose of Sorafenib is 400 mg (200 mg twice a day) atleast 1 hour before or 2 hours after a meal.

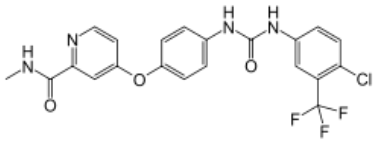

Figure 2: Chemical Structure

2.2 Mechanism of action

Sorafenib is a protein kinase inhibitor that decreases tumor cell proliferation in vitro. Sorafenib was shown to inhibit multiple intracellular (CRAF, BRAF and mutant BRAF) and cell surface kinases (VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR-ß). Several of these kinases are thought to be involved in tumor cell signaling, angiogenesis, and apoptosis. Sorafenib inhibited tumor growth and angiogenesis of human hepatocellular carcinoma and renal cell carcinoma

2.3 Pharmacological actions

Sorafenib was highly efficacious in vivo in renal tumour xenograft models (RENCA model). Antitumor efficacy was also demonstrated in vivo in a number of different non-renal tumour Xenograft models by affecting the RAS/RAF/MEK pathway. This included xenograft models of human colon, lung, breast, melanoma, leukemia, pancreas and ovary. The efficacy of Sorafenib against this tumour models suggested that a RAF kinase inhibitor may have utility not only in human tumours containing RAS and/or b-RAF mutations, but also in tumours that over express other growth factor receptors that signal through the same pathway.

Furthermore, Sorafenib was very effective against the MV4-11 AML model that expresses an activating Flt3 mutation. In cellular assays in vitro, sorafenib inhibited the RAF/MEK/ERK pathway in breast, pancreatic, melanoma, and colon tumour lines as evidenced by reduction of phospho-ERK levels including cell lines expressing either wild-type or mutant k-RAS or BRAF. However, inhibition of the RAF/MEK/ERK pathway was not observed in the non-small cell lung cancer (NSCLC) lines A549 and H460, at concentrations up to 20 µm sorafenib. The mechanism underlying the lack of Inhibition of ERK phosphorylation in these cell lines has not been elucidated. No direct comparison was made non-clinically between a tumour model that expresses a wild type VHL and a VHL mutant sub line of the same model.

Sorafenib was active against the 786-0 human renal tumour model that has a VHL deletion and was less active against the CAKI-1 human renal tumour model that expresses wild type VHL. However, since these two tumour lines were derived independently from separate patients, it could not be concluded that the difference in VHL status was solely responsible for the different sensitivity to sorafenib. Although this data could help to predict the sensitivity of a human tumour to sorafenib therapy, limited data did not support patient selection for sorafenib treatment based on this biomarker. The results suggested that sorafenib can be combined with paclitaxel, irinotecan, gemcitabine, gefitinib and cisplatin with no significant increase in the toxicity and without diminishing their antitumor efficacy. However, the combination of sorafenib and doxorubicin required reduction of the dose level of both agents to attain acceptable tolerance and efficacy.

2.4 Pharmacokinetics of Sorafenib

Absorption

Following oral administration, sorafenib reaches peak plasma levels in approximately 3 hours. When given with a moderate-fat meal, bioavailability was similar to that in the fasted state. With a high-fat meal, sorafenib bioavailability was reduced by 29% compared to administration in the fasted state.

Distribution

In vitro binding of Sorafenib to human plasma proteins is 99.5%. Human serum albumin, α-globulin and the low density lipoprotein are the main binding proteins. Sorafenib was equally distributed between plasma and blood cells.The binding of Sorafenib to plasma is dependent on pH. The fraction unbound decreased to 0.165% at pH 7.99 and increased to 1.80% at acidic pH 6.78.

Metabolism

Sorafenib is metabolized primarily in the liver, undergoing oxidative metabolism, mediated by CYP3A4, as well as glucuronidation mediated by UGT1A9. Sorafenib accounts for approximately 70-85% of the circulating analytes in plasma at steady-state. Eight metabolites of sorafenib have been identified, of which five have been detected in plasma as N-oxide, shows in vitro potency similar to that of sorafenib. This metabolite comprises approximately 9-16% of circulating analytes at steady-state.

Excretion

Following oral administration of a 100 mg dose of a solution formulation of sorafenib, 96% of the dose was recovered within 14 days, with 77% of the dose excreted in feces, and 19% of the dose excreted in urine as glucuronidated metabolites. Unchanged sorafenib, accounting for 51% of the dose, was found in feces but not in urine.

2.5 Drug Interactions

The drugs namely Docetaxel, doxorubicin and Fluorouracil requires adjustment of dose when co-administered with sorafenib.

2.6 Adverse Drug Reactions

Hand-foot skin reaction and rash represent the most common adverse reactions attributed to sorafenib. They generally appear during the first six weeks of treatment .Permanent discontinuation of therapy due to hand-foot skin reaction may be required in few cases.

2.7 Over dosage

There is no specific treatment for intake of overdose. The highest dose studied clinically is 800 mg twice daily. The adverse reactions observed at this dose were primarily diarrhea and dermatologic. No information is available on symptoms of acute overdose in animals because of the saturation of absorption in oral acute Toxicity studies conducted in animals. In cases of suspected overdose, sorafenib should be withheld and supportive care instituted.

2.8 Therapeutic Indications

Sorafenib is indicated for the treatment of patients with advanced renal cell carcinoma, hepatocellular carcinoma (HCC) and Differentiated thyroid carcinoma (DTC) that is refractory to radioactive iodine treatment.

3. Use in specific populations

3.1 Pregnancy

Based on its mechanism of action and findings in animals, Sorafenib caused embryo-fetal toxicities in animals at maternal exposures that were significantly lower than the human exposures at the recommended dose of 400 mg twice daily. There are no adequate and well-controlled studies in pregnant women using the drug. The effects occurred at doses considerably below the recommended human dose of 400 mg twice daily (approximately 500 mg/m /day on a body Surface area basis). Adverse intrauterine development effects were seen at doses ≥0.2 mg/kg/day (1.2 mg/m /day) in rats and 0.3 mg/kg/day (3.6 mg/m /day) in rabbits.

3.2 Nursing Mothers

It is not known whether sorafenib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from sorafenib, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Following administration of radio labeled sorafenib to lactating Wistar rats, approximately 27% of the radioactivity was secreted into the milk. The milk to plasma AUC ratio was approximately 5:1.

3.3 Pediatric Use

The safety and effectiveness of Nexavar in pediatric patients have not been studied. repeated dosing of sorafenib to young and growing dogs resulted in irregular thickening of the femoral growth plate at daily sorafenib doses ≥ 600 mg/m (approximately 0.3 times the AUC at the recommended human dose), hypocellularity of the bone marrow adjoining the growth plate at 200 mg/m /day (approximately 0.1 times the AUC at the recommended human dose), and alterations of the dentin composition at 600 mg/m /day. Similar effects were not observed in adult dogs when dosed for 4 weeks or less.

3.4 Geriatric Use:

In total, 59% of HCC patients treated with Nexavar were age 65 years or older and 19% were 75 and older. In total, 32% of RCC patients treated with Nexavar were age 65 years or older and 4% were 75 and older. No differences in safety or efficacy were observed between older and younger Patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

4. Conclusion

The long-term treatment with sorafenib is associated with continued efficacy and a well-tolerated safety profile. It can be used in combination with other antineoplastic drugs effectively. Sorafenib was teratogenic and induced embryo-fetal toxicity. However treatment with sorafenib prolongs progression-free survival in patients with advanced clear cell renal cell carcinoma in whom previous therapy has failed.

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