SORAFENIB-MULTIKINASE INHIBITOR FOR ADVANCED RENAL CELL CARCINOMA.

Aruna Bhushan[1] ., Theophilus V Bhushan[2]., Haslikar.N[1] .

1. Department of Pharmacology, B.I.M.S, Belgaum-590001, Karnataka. India

2. Department of Surgery, B.I.M.S, Belgaum-590001, Karnataka. India

Summary

The five years survival rate for a patient with advanced renal cell carcinoma is less than 10%. High doses of interleukin-2 therapy, interferon alfa provides rarely a durable complete response and survival advantage. Sorafenib an orally active multikinase inhibitor, targeting the Raf/Mek/Erk pathway showed promising results by prolonging progression-free survival in patients with advanced renal cell carcinoma in whom previous therapy had failed, or who are unable to tolerate cytokines. Sorafenib also showed good safety profile with moderate and easily manageable toxic effect when compared with conventional chemotherapy.

Key words: Renal cell carcinoma, Sorafenib, Multikinase inhibitor

Corresponding Author,
Dr.Aruna Bhushan,
Associate Professor,
Department of Pharmacology,
Belgaum institute of Medical Sciences,
Belgaum-590001
Karnataka, INDIA.
E-mail: **arunamarina@yahoo.co.in**

Introduction

Renal cell carcinoma (RCC) is the most common primary renal malignancy in adults arising from proximal renal tubule. It accounts for approximately 85% of renal tumors and 2% of all adult malignancies [1,2] and it occurs in patients aged between 50-70 years. Renal cell carcinoma affects about 3 in 10,000 people, resulting in about 38,890 new cases and 12,000 deaths every year in United States. Initial treatment strategy is most commonly a radical or partial nephrectomy.

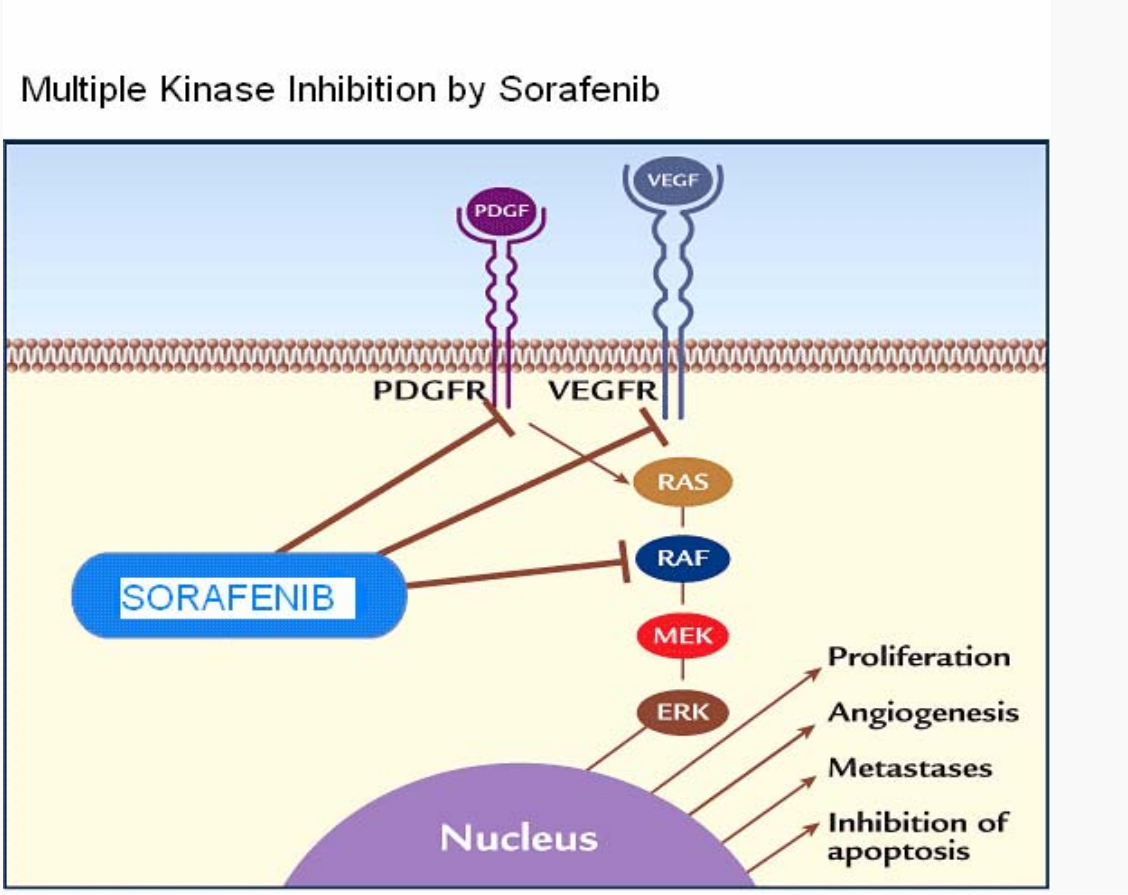
The five year survival is 60-70% but this is lowered considerably where metastases have occurred. RCC is resistant to radiation therapy and chemotherapy [3,4], although some cases respond to immunomodulating therapies, such as cancer vaccines and interleukin-2, but with substantial toxicity. This new targeted cancer therapy sorafenib, the first receptor tyrosine kinase (RTK) inhibitor and was FDA approved in December 2005. Also designated as "Fast Track" by FDA[5]. It is a small molecular inhibitor that targets serine/threonine and receptor tyrosine kinases which interferes with tumor growth by inhibiting angiogenesis as well as tumor cell proliferation. It targets RAF kinase, PDGFR-b (platelet derived growth factor), VEGFR-2, VEGFR-3 Kinases, FLT-3, RET and cKIT the receptor for stem cell factor [6,7]. Studies have shown that it prolongs progression-free survival in patients with advanced clear cell carcinoma in whom previous therapy has failed.

Pathogenesis

Vascular endothelial growth factor (VEGF) known as vascular permeability factor, also plays a role in endothelial proliferation [8]. VEGF is overexpressed in renal cell carcinoma (RCC). VEGF overexpression in RCC is due to inactivation of the von Hippel-Lindau tumor suppressor gene (*VHL*) [9,10]. Loss of VHL protein (pVHL) expression results in constitutive expression of HIF-1α and induction of hypoxia-regulated genes, VEGF, platelet-derived growth factor-β (PDGF-β), and transforming growth factor-α (TGF-α)[11].

When VEGF and PDGF the growth factor binds to a receptor located on the cell's surface, a series of subsequent events take place within the cell. Specifically, the ras protein is activated and in turn activates raf. Raf then activates MEK, which is an activator of map kinases (ie: Erk) that ultimately trigger cell proliferation. This process, by which a message from outside the cell is delivered through the surface and into the cell, is referred to as receptor-mediated cell signaling. The genes and Ras/Raf/MEK/Map kinase signaling pathway have been implicated in the malignant phenotype of RCC, which is characterized by hypervascular tumors, local and distant metastases via hematogenous spread, uncontrolled growth, and resistance to apoptosis[9,12].

Sorafenib orally administered inhibitors of protein tyrosine kinases activity of more than one receptor. Inhibits these intracellular tyrosine kinases and blocks signal transduction after a growth factor, cytokine, or other ligand binds to the receptor's extracellular domain. Thus it inhibits tumor growth, metastasis, or angiogenesis (fig 1).



Pharmacokinetics

Sorafenib after oral administration, the mean relative bioavailability is 29-49% reaches the peak plasma levels in approximately 3 hours. Diet rich in fat reduces its absorption by 29% compared to administration in the fasted state. It is recommended to be administrated 1 hour before or 2 hours after food. Multiple dosing for 7 days resulted in a 2.5 to 7 fold accumulation compared to single dose administration and steady state plasma concentration is achieved within 7 days, with a peak-to- trough ratio of mean concentration of less than 2.

Sorafenib is metabolized in liver primarily by oxidation mediated by Cyp3A4 enzyme and glucuronidation by UGT1A9. Eight metabolites have been identified, of which five have been detected in plasma, pyridine N-oxide 9-16% is main circulating metabolite in plasma with potency similar to sorafenib. The apparent plasma clearance after oral administration of 100mg is 77% in faeces and 19% in urine as glucuronidated metabolite. The mean elimination half life is 25-48 hours.

Sorafenib does not require dose adjustment for age or gender as no clinically significant differences exist in the plasma concentration. But in patient with severe hepatic and renal insufficiency it has to be administered cautiously.

Adverse effects

The result of various clinical trials indicated these incidences as commonly observed side effects with sorafenib treatment were rash, hand-foot skin reaction, diarrhea and hypertension. There are other reports of bleeding problems, mouth sores, weakness, nausea and vomiting [13].

Drug interactions

Sorafenib is metabolized by Cyp3A4 and UGT1A9 pathway. Ketoconazole a potent inhibitor of Cyp3A4, co-administered with sorafenib did not alter its mean AUC. Sorafenib is a competitive inhibitor of Cyp2C19, Cyp2D6 and Cyp3A4, it also did not alter when concomitantly administered with omeprazole, dextromthorphan and midazolam.

There is no clinical information on the effect of Cyp3A4 inducers on the pharmacokinetic of sorafenib. Substance that are inducers of Cyp3A4 activity namely rifampin, St.John's wort, phenytoin, phenobarbitone, carbamazepine and dexamethasone are expected to increase metabolism and thus decrease sorafenib concentrations.

In clinical studies, sorafenib administered with anticancer drugs including gemcitabine, oxalipltin, doxorubicin and irinotecan. It had no effect on the pharmacokinetic of gemcitabine or oxaliplatin, there was 21% increase in the AUC of doxorubicin and irinotecan, whose active metabolite SN-38 is further metabolized by the UGT1A1 pathway, there was a 67-120% increase in the AUC of SN-38 and 26-42% increase in the AUC of irinotecan. Caution is recommended when administering sorafenib with compounds that are metabolized or eliminated by UGT1A1 pathway.

Sorafenib also increases the systemic exposure to substrates of Cyp2B6 and Cyp2C8 when co-administered with it.

Dosage and administration

Sorafenib(NEXAVAR) Daily dose 400mg (2 x 200mg tablets) twice daily, before food or 2 hours after food. Treatment is continued until no longer clinical benefit from therapy or unacceptable toxicity. The dose can be reduced to 400mg once daily.

Preclinical / Clinical trails

Sorafenib has antitumor activity in animal model[6]. In the murine renal adenocarcinoma model[14] and the Von Hippel-Lindau tumor suppressor gene(VHL) knock out model[15]. Sorafenib prevented tumor growth primarily by inhibiting angiogenesis. It also induced tumor cell apoptosis and necrosis in VHL-deficient xenograft model[15].

In an international, multicenter randomized trial with the primary endpoints of progression-free survival and OS, 769 patients were stratified by the Memorial Sloan-Kettering Cancer Center prognostic risk category and by country and were randomly assigned to receive either sorafenib (400 mg b.i.d.) or a placebo. Approximately 82% of the patients had received prior IL-2 and/or interferon in both arms of the study.

The median progression-free survival for patients randomly assigned to sorafenib was 167 days, compared with 84 days for patients randomly assigned to placebo (P <.001). The estimated HR for the risk of progression with sorafenib compared with a placebo was 0.44 (95% CI, 0.35–0.55). Results for OS (overall survival) are not yet available. [16].

Sorafenib is currently licensed for advanced Renal Cell Carcinoma. when cytokines have failed or are unsuitable and has shown to increase median progression free survival (PFS) from 2.8 months to 5.5 months versus placebo (p<0.001) in the Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET) study, published in the New England Journal of Medicine[17].

Overall survival (OS) results for the kidney cancer TARGET study were presented at ASCO. The TARGET study was a multi-national, randomised, placebo-controlled Phase III study of sorafenib administered as a single agent. More than 900 patients with advanced RCC, who had previously failed one prior systemic therapy, were enrolled in 117 sites worldwide and randomised into two treatment arms to receive either 400 mg sorafenib or placebo twice a day. Median OS was 17.8 months in sorafenib-treated patients compared to 15.2 months in those taking Placebo.4(HR=0.88; p=0.146).**4

TARGET study investigator Tim Eisen, Professor of Medical Oncology, Cambridge added; "The results of the interim analysis were sufficiently compelling - a doubling of Progression Free Survival (PFS) for the sorafenib patients - and all patients still in the placebo arm of the study were offered the opportunity to cross over onto sorafenib. This was done to allow all patients in the trial to benefit from the drug, despite the likelihood that the crossover of patients would confound the overall survival results of the trial. Nearly all of those who could cross over did so. Even those patients who started taking sorafenib late in the day appear to have benefited from treatment. The final overall survival data resulting from the TARGET study are consequently difficult to interpret"[16]

In a phase 2, randomized discontinuation trial, in patients with metastatic renal cell carcinoma in whom previous treatment had failed. Sorafenib prolonged progression free survival as compared with placebo [18].

Conclusions

Oral sorafenib appears to be a promising drug which prolongs progression-free survival in patients with advanced renal cell carcinoma in whom the cytokines have failed or are unsuitable. In clinical trials, this drug showed a good safety profile. But caution is required for potential interaction when co-administered with certain drugs. Cost-benefit of this drug also should be considered before prescribing to the patients.

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