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Review Article

REGORAFENIB (STIVARGA): A NEW OPTION IN THE TREATMENT OF PATIENTS WITH METASTATIC COLORECTAL CANCER (CRC)

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ABSTRACT

The American Cancer Society estimates that in 2011 about 141,210 people will be diagnosed with colorectal cancer and about 49,380 people will die of the disease in the US. Over the past 8 to 10 years, significant advances have been made in the treatment of metastatic colorectal cancer (mCRC). It has been approved by US FDA on septenber 27, 2012. Regorafenib is an orally administered multikinase inhibitor. It shows non-specific binding to several intracellular kinases, with potent inhibitory activity against vascular endothelial growth factor receptors 1—3 (VEGFR1, VEGFR2 [KDR], and VEGFR3 [FLT4]), PDGFRB, FGFR1, RAF, TIE2, and the mutant oncogenic kinases KIT, RET, and BRAF. Commonly reported (> 10%) adverse effects include fatigue, hand-foot skin reaction, diarrhea, hepatotoxicity, hemorrhage, hypertension, cardiac ischemia and infarction etc. Patients were randomly assigned in a 2:1 ratio to regorafenib or placebo with a computer-generated randomization list prepared by the study sponsor.

Keywords: Colorectal cancer, Regorafenib, VEGFR, CYP3A4, PFS, OS, Phase III trials

INTRODUCTION

Colorectal cancer is cancer that starts in the colon or the rectum. These cancers can also be referred to separately as colon cancer or rectal cancer, depending on where they start [1]. Rectal bleeding and anemia are symptoms of colorectal cancer cause adverse effect such as weight loss and changes in bowel habits. Most colorectal cancer occurs due to lifestyle and increasing age with only a minority of cases associated with underlying genetic disorders. It typically starts in the lining of the bowel and if left untreated, can grow into the muscle layers underneath, and then through the bowel wall [2, 3].

Table 1: Incidence rates of colorectal cancer in various countries

Country	Male	Female
India	4.3	3.4
Bangladesh	4.5	4.0
Pakistan	4.9	4.2
Afghanistan	6.9	7.0
Sri Lanka	7.5	5.8
China	16.3	12.2
Japan	41.7	22.8
Singapur	41.6	28.3

Country Incidence rates per 100,000a

a Age adjusted rates for world standard population [8, 9,10]

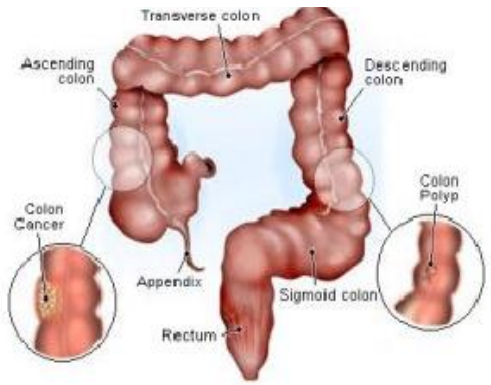

Fig. 1: Physiology of colon and rectum in human body

(Source: http://www.daviddarling.info/images/colon_cancer.jpg)

Other symptoms are pain in the lower stomach, dark-or-black coloured stools, a change in the shape of the stools, new onset of constipation or diarrhea that last for more than a few days. In both men and women, colorectal cancer is the third most commonly diagnosed cancer and the third leading cause of cancer death [4, 5, 6]. The American Cancer Society estimates that in 2011 about 141,210 people will be diagnosed with colorectal cancer and about 49,380 people will die of the disease in the US [7]. Within Asia, the incidence rates of CRC vary widely and are uniformly low in all south Asian countries and high in all developed Asian countries [8].

Factor affecting colorectal cancer

Age

The incident of colorectal cancer is found to be more in case of aged population than in younger population. Overall, 90% of new cases and 94% of deaths occur in individuals 50 and older.

Sex

Incidence and mortality rates of colorectal cancer are about 35% to 40% higher in men than in women.

Race/ethnicity

Incidence and mortality rates of colorectal cancer are highest in African American men and women; incidence rates are 20% higher and mortality rates are about 45% higher than those in whites. Incidence and mortality rates among other major racial/ethnic groups are lower than those among whites [11].

Regorafenib is administerd orally. Regorafenib demonstrated to increase the overall survival of patients with metastatic colorectal cancer who have previously received combination chemotherapy (specially fluropyrimidine, oxaliplatin, and irinotecan based regimens) and therapy against vascular endothelial growth factor receptor (VEGFR). It has been approved by US FDA on septenber 27, 2012. Its commercial name is stivarga. It is an oral multi-kinase inhibitor developed by Bayer which targets angiogenic, stromal and oncogenic receptor tyrosine kinase (RTK). Regorafenib shows anti-angiogenic activity due to its dual targeted VEGFR2-TIE2 tyrosine kinase inhibitor [12].

Regorafenib is currently being studied for treatment of a variety of other cancers, including: hepatocellular carcinoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma [13, 14].

Chemical structure

Fig. 2: Chemical structure of Regorafenib

The chemical name of regorafenib is 4-(4-(3-(4-chloro-3-(trifluoromethyl)phenyl)ureido)-3-fluorophenoxy)-N-methylpicolinamide. Its chemical formula is $C_{21}H_{15}ClF_4N_4O_3$ and molecular weight is 482.08. Regorafenib is a monohdrate and it is slightly soluble in ethyl acetate, ethanol, methanol, acetonitrile and insoluble in water [15].

Mechanism of action

Regorafenib is a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases [16] with potent preclinical antitumor activity. VEGFR2 and tyrosine kinase with immunoglubulin and epidermal growth factor homology domain 2 play crucial roles in the bilogy of normal and tumor vasculature. Regorafenib inhibits this endothelial cell kinase in biochemical and cellular kinase phosphorylation assays. Furthermore, regonaferib inhibits additional angiogenic kinase (VEGFR1-3, platelete-derived growth factor receptor-β and fibroblast growth factor receptor1) and the mutant oncogenic kinase KIT, RET and BRAF. In in vivo models, regorafenib demonstrated anti-angiogenic activity in a rat tumor model, and inhibition of tumor growth as well as anti-metastatic activity in several mouse xenograft models including some for human colorectal carcinoma [15, 17, 18].

Fig. 3: Schematic mechanism of Regorafenib [15, 18]

Pharmacokinetics [19]

Absorption

Peak plasma concentration occur a median of 4 hours after oral administration. When give with a high-fat meal, drug exposure increases 48% for regorafenib, but decreases 20% for M-2 and decreases 51% for M-5, compaired with fasting condition. When administered with low fat meal, drug exposure increases 36% for regorafenib, 40% for M-2 and 23% for M-5, compaired with fasting conditions. According to FDA, Pharmakokinetic information of regorafenib is following below when patients with advanced solid tumors received a single 160 mg dose of stivarga.

Table 2: Properties of Regorafenib

Property	Regorafenib
C_{max}	2.5µg/mL
AUC	70.4µg*h/ml
Bioavailability	69% to 83%

Distribution

Plasma-protein binding is high for regorafenib (99.5%), M-2 (99.8%), and M-5 (99.5%). It undergoes enterohepatic circulation.

Metabolism

CYP3A4 and UGTIA9 are metabolic enzymes and is resposible for metabolism of regorafenib.

Elimination

The drug is eliminated primarily in the feces unchanged (47% of dose) and as metabolites (24% of dose). The remaining 19% is eliminated in the urine. The mean elimination half life is 28 hours for regorafenib, 25 hours for M-2, and 51 hours for M-5.

Hepatic and renal impairment

No dosage adjustment is necessary in patients with mild renal impairment, or mild to moderate hepatic impairment; use caution in these patients. Avoid use in severe hepatic impairment. Regorafenib

has not been studied in severe renal impairment, and data are limited in moderate renal impairment. Regorafenib monotherapy for previously treated metastatic colorectal cancer, randomised, placebo controlled, phase 3 trial

Patients were randomly assigned in a 2:1 ratio to regorafenib or placebo with a computer-generated randomisation list prepared by the study sponsor. A randomized, double-blind trial compared regorafenib 160 mg/day (n=505) and placebo (n=255) in patients with previously treated metastatic colorectal cancer. Both treatments were given for 21days of each 28 day cycle in addition to best supportive care. The primary outcome of median overall survival was prolonged with regorafenib (6.4 months) compared with best supprtive care alone (5 months, p=0.0102). Median proression-free survival was also prolonged by regorafenib (2 months) compaired with best supportive care alone (1.7 months, p<0.001). Overall response rate was similar with regorafenib (1%) or best supportive care alone (0.4%).

Fig. 4: Trial profile [15, 17, 18]

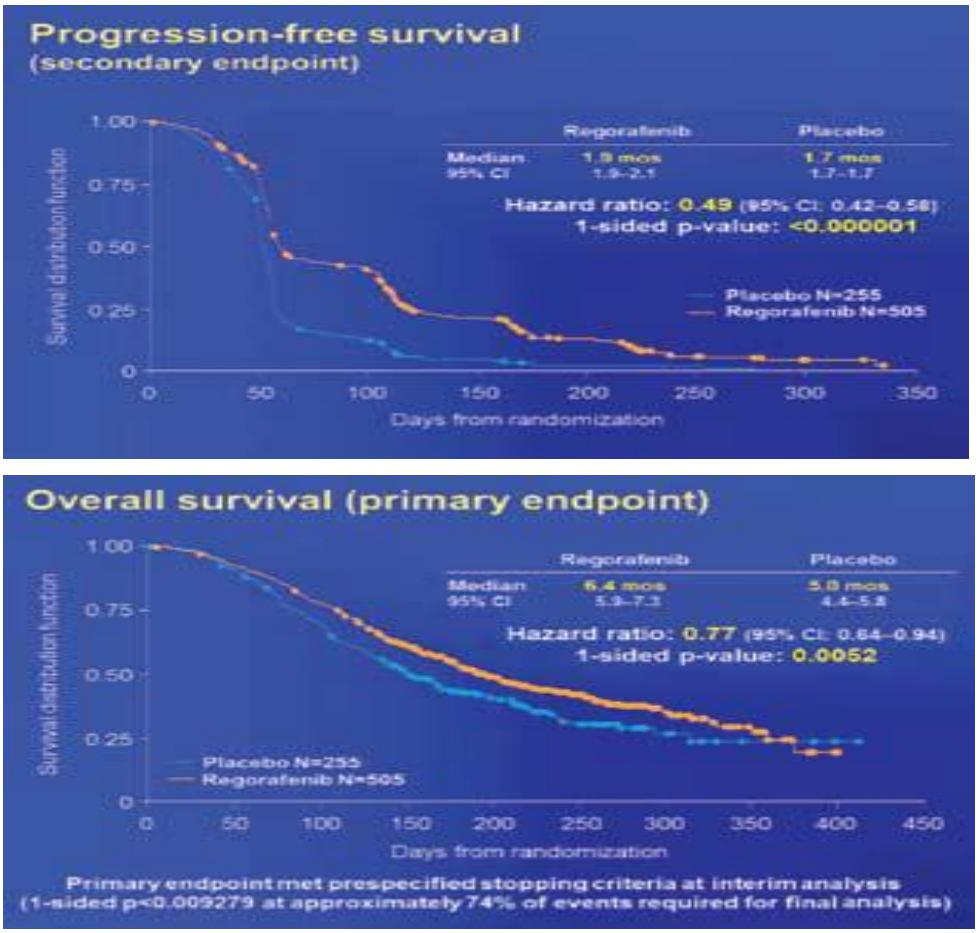

Fig. 5: PFS & OS curve [20]

Drug-drug interactions [19]

(i) Rifampin is a strong CYP3A4 inducer and it decreased regorafenib exposure 50%, and it increased M-5 exposure 264%; M-2 exposure was unchanged.

(ii) Avoid concomitant administration of regorafenib with strong CYP3A4 inhibitors (eg-azole antifungals, clarithromycin, grapefruit juice, telethromycin) or strong CYP3A4 inducers (eg-carbamazepine, phenobarbital, phenytoin, refampin).

(iii) Ketoconazole is a strong CYP3A4 inhibitor and it increasedregorafenib exposure 33% but decreased exposure to M-2 and M-5 by 23%.

(iv) Regorafenib is an inhibitor of ABCG2 (Breast cancer resistant protein) and ABCB1 (p-glycoprotein).

(v) Regorafenib, M-2, and M-5 inhibits UGT1A9 and UGT1A1 at therapeutically relevant concentrations.

Adverse reaction [11, 21, 22]

Dose modifications may be necessary for serious adverse reactions including hepatotoxicity, hemorrhage, dermatological toxicity, hypertension, cardiac ischemia and infarction, reversible posterior leukoencephalopathy syndrome (RPLS), and gastrointestinal perforation or fistula. The most common adverse effects were asthenia/fatigue, decreased appetite and food intake, hand-foot-skin reaction (HFSR)/palmar plantar erythrodysesthesia (PPE), diarrhea, mucositis, weight loss, infection, hypertension and dysphonia.

1. ***Hepatotoxicity-*** Severe and sometimes fetal hepatotoxicity has been observed in clinical trials. Liver biopsy showed hepatocyte necrosis with lymphocyte infiltration. In clinical trials, hepatic failure occurred in 1.6% patientsin the regonaferib arm and 0.4% of patients in the placebo arm. Monitor hepatic function prior to and during treatment. Interupt and then reduce or discontinue stivarga for hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis.

2. ***Hemorrhage-*** In clinical trials, stivarga was associated with an increased incidence of hemorrhage, including fetal hemorrhage. In this trial, hemorrhage occurred in 21% of patients in the regorafenib arm and 80% of patients in the placebo arm. Permanently discontinue stiverga in patients with severe or life-threatening hemorrhage.

3. ***Dermatological Toxicology-*** Hand–foot skin reaction (palmar–plantar erythrodysesthesia) and rash are the most frequently observed dermatological reactions with regorafenib. Therapy should be temporarily withheld and then reduced or discontinued permanently, depending on the severity and persistence of dermatological toxicity. Supportive measures for symptomatic relief should be initiated.

4. ***Hypertension-***Elevations in blood pressure (BP) have been observed with regorafenib. Therapy should not begin until BP is controlled. BP should be monitored weekly for the first 6 weeks and then during every cycle or more frequently as clinically indicated. Regorafenib should be temporarily or permanently withheld in cases of severe or uncontrolled hypertension.

5. ***Cardiac ischemia and infarction-*** Regorafenib has been associated with an increased incidence of myocardial ischemia and myocardial infarction (MI). The drug should be withheld if new or acute cardiac ischemia or an MI occurs. Therapy should be resumed only after the event is resolved.

6. ***Reversible posterior leukoencephalopathy syndrome (RPLS) -*** This syndrome has been reported with regorafenib. If the diagnosis of RPLS is confirmed with magnetic resonance imaging, regorafenib should be discontinued.

7. ***Gastrointestinal perforation or fistula-*** GI perforation and fistula have been reported in patients receiving regorafenib. Therapy should be permanently discontinued if GI perforation or fistula develops.

8. ***Wound-healing complications-*** Regorafenib should be stopped at least 2 weeks before scheduled surgery but may be resumed if wound healing is considered to be adequate. Therapy should be discontinued in patients with wound dehiscence.

9. ***Embryofetal toxicity complications-*** Regorafenib can cause fetal harm when administered to pregnant women. If the patient is using this drug during pregnancy or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus.

Supplied, storage and handling [19]

A package containing three bottles is used for supplied stivarga tablets. Each bottle containing 28 tablets, for a total of 84 tablets per package. Stivarga tablets are stored tightly closed original bottle. 25^0C is suitable temperature for stored stivarga. After first opening keep the bottle tightly.

Dosage and administration

The recommended dose is 160mg once daily for the first 21 days of each 28-day cycle. It is administered orally. The drug is administered at the same time each day [19].

Non-clinical toxicology

Studies regarding the carcinogenicity of Regorafenib have not been examined. Regorafenib doesn't have any genotoxicty in the in-vitro or in the in-vivo study but a major active metabolite of regorafenib, i.e, M-2 demonstrate a positive clastogenicity which in turn causes an aberration in Chinese hamster V79 cells.

Studies examined that the impairment in fertility due to regorafenib have not been conduct; however tubular atrophy , degeneration in the testes, atrophy in seminal vesicle, cellular debris and oligospermia in the epididymides is being observed in case of male rats at a dose similar to human dose in the clinical study based on AUC. In case of female rats there is an increase in the necrotic corpora lutea in the ovaries is observed at the same dose [19].

Special populations [19]

Based on the mechanism of action of regorafenib, it causes a fetal harm in pregnant woman. Regorafenib was found to have teratogenic and embryolethal effect in rats and rabbits when exposed to dose lower than the human dose, with an increase in incidence like cardiovascular dysfunction, genitourinary and skeletal malformation. If this drug is being administered in pregnant woman or if a woman gets pregnant while talking this drug then the patient should be prepared to have a potential hazard to the fetus.

In the embryological-fetal development study is being observed that, a total loss of pregnancy i.e. 100% resorption of litter is seen in rat at a dose of 1mg/kg (based on body surface area) and in rabbits at doses as low as 1.6 mg/kg. Now in the distribution study of pregnant rats where single dose is administered there is an increase in the penetration of regorafenib across the blood-brain barrier in fetus as compared to dams.

In the repeated dose study where a pregnant rats is being administered with regorafenib daily ventricular septal defects seems to occur even at lowest tested dose of 0.4mg/kg. Regorafenib when administered in a dose of ≥0.8mg/kg results in dose-dependent increase in the incident of additional cardiovascular dysfunction and skeletal abnormalities along with adverse effect on the urinary system which includes missing of kidney/urethra, deformation and malpositioning of kidney and also causes hydronephrosis.

In case of nursing mothers the effect of regorafenib is found to be unknown; however it is found that few of its active metabolites as found to be excreted out through human milk so the administration of regorafenib in case of nursing mothers seems to have an adverse effect on their young ones.

The efficacy and safety of regorafenib in case of pediatrics population have not been established; however in a repeated dose study in rats of 28-day a dose dependent incident of dentin alteration and angiectasis occurred. These incidents were observed

at a dose which is as low as 4mg/kg (approx.25%of the AUC in humans recommended dose). The same results was observed at 13-week of repeated dose study of regorafenib in dogs. Therefore the administration of regorafenib in case of animals leads to the persistent growth and thickening of the femoral epiphysis growth plate.

CONCLUSIONS

It is concluded that regorafenib is a new first oral multikinase inhibitor developed by Bayer which targets angiogenic, stromal and oncogenic receptor tyrosine kinase (RTK) with proven activity in mCRC. A phase 3 trial of regorafenib versus placebo is ongoing to define more fully the safety and efficacy of regorafenib. Regorafenib increases OS in patients with mCRC that has progressed current standard therapies. Regorafenib is a new potential standard of care for patients with chemorefratory mCRC.

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