KDR gene as a Predictive Biomarker of Response to Regorafenib in Patients with Metastatic Colorectal Cancer (mCRC)

Srinivasa BJ1, Lalkota Bhanu Prakash1*, Nasiruddin M2 and Radheshyam N1

1Department of Medical Oncology, HCG Speciality Centre, Bangalore, India
2Department of Molecular Pathology, Triesta Reference Laboratory, Bangalore, India

Corresponding author: Lalkota Bhanu Prakash, Department of Medical Oncology, HCG Speciality Centre, Bangalore, India, Tel: 09739699388; E-mail: bhanu.lalkota@gmail.com

Srinivasa BJ, Department of Medical Oncology, HCG Speciality Centre, Bangalore, India, E-mail: sripav77@yahoo.co.in

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Abstract

Background: Regorafenib is an oral diphenyl urea multikinase inhibitor which is anti-angiogenic, and has shown promising anti-tumor activity in Metastatic Colorectal Cancer (mCRC). Reports have shown that response to regorafenib is more favourable in patients with KDR gene mutation. This study correlates KDR gene mutation as an ideal predictive biomarker to regorafenib (Tyrosine Kinase Inhibitor) attempts to correlate response in metastatic colorectal cancer (mCRC).

Methods: This is a single centre prospective analysis of total 9 patients at HCG cancer speciality centre, Bengaluru, India. The median age of 9 patients was 54 years (21-71 years). 5 patients were male and 4 patients were female, 6 patients are African and 3 were Indian. KRAS gene was found to be mutated in 6 patients and wild type in 3 patients. Out of 9 patients, 6 have received FOLFOX-4 chemotherapy+Biological for 6 cycles and 3 patients received FOLFIRI chemotherapy+Biological for 3 cycles as 1st line treatment. These patients received tab Regorafenib as 3rd line treatment. For all patients 48 Gene panel was done, which includes extended RAS and KDR gene mutation analysis.

Results: Analysis at the end of 3 months of treatment, 2 patients had PR, 1 patient had SD, 5 patients had PD and 1 patient defaulted. There was no correlation of response with KRAS mutational status. KDR (VEGFR-2) was wild type in all the patients. With regards to safety, the drug was well tolerated by all patients and no one withdrawn because of adverse effects. Conclusions: Absence of KDR gene mutation may not respond to regorafenib treatment in MCRC. To predict KDR gene mutation as a biomarker, large number of studies with mutated KDR gene is required.

Keywords: KDR; Regorafenib; KRAS; MCRC

Introduction

Colorectal cancer is a major cause of morbidity and mortality throughout the world. It accounts for over 9% of all cancer incidences [1,2]. Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the fourth leading cause of cancer-related deaths in the world, and its burden is expected to increase by 60% to more than 2.2 million new cases and 1.1 million cancer deaths by 2030 [3]. In India, the annual incidence rates (AARs) for colon cancer and rectal cancer in men are 4.4 and 4.1 per 100000, respectively [ICMR data 2014]. CRCs most commonly metastasize to the liver, lung and peritoneum, but various other metastatic sites such as bone, spleen, brain and distant lymph nodes have been described [4]. The mCRC-related 5-year survival rate approaches 60% [5].

In 2012 Food and Drug Administration approved regorafenib for the treatment of patients with Metastatic Colorectal Cancer (mCRC) who have been previously treated with fluoropyrimidine, oxaliplatin, and irinotecan based chemotherapy, an anti VEGF therapy, and, if KRAS wild type, an anti EGFR therapy[7].

Regorafenib, an oral multikinase inhibitor, its active metabolites inhibit multiple membrane-bound and intracellular kinases that are involved in normal cellular functions and pathologic processes, including those in the RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-alpha, PDGFR-beta, FGFRI, FGFRII, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, BRAFV600E, SAPK2, PTK5, and Abl pathways [6-8]. The recommended dose and schedule for regorafenib is 160 mg (four 40 mg tablets) orally once daily for the first 21 days of each 28 day cycle.

VEGF, also known as VEGF-A, is a protein with vascular permeability activity that was originally purified from a fluid secreted by a tumor. The VEGF family includes VEGF-A, VEGFB, VEGFC, VEGF-D, PlGF (placental growth factor), VEGF-E (Orf-VEGF), and Trimeresurus flavoviridis svVEGF. VEGF-A binds to and activates both VEGFR-1 and VEGFR-2, promoting angiogenesis, vascular permeability, cell migration and gene expression [9].

The VEGFR- 2 coded by the gene KDR (located in 4q12) is the predominant mediator of VEGF-stimulated endothelial cell functions, including cell migration, proliferation, survival, and enhancement of vascular permeability. VEGFR-2 exhibits robust protein tyrosine kinase activity in response to the VEGF ligand [10].
KDR (Kinase insert Domain Receptor)/VEGFR-2 functions similarly to most tyrosine kinase receptors: it dimerises and is autophosphorylated on several cytoplasmic tyrosine residues upon ligand binding. KDR is thought to be principally responsible for VEGF signalling to stimulate the proliferation, chemotaxis, survival, and differentiation of endothelial cells and to alter their morphology; moreover, KDR signalling is thought to stimulate vessel permeability and vessel dilation [11].

Jauhari et al. [12], reported 19.6% of KDR gene mutation in 112 FFP samples of colorectal cancer patients by Next Generation Sequencing (NGS).

Current study attempts to correlate KDR gene mutation as an ideal predictive biomarker to the response of regorafenib (Tyrosine Kinase Inhibitor) in Metastatic Colorectal Cancer (MCRC).

Procedure
This is a single centre prospective analysis of total 9 patients; analysis was done in order to access PFS and tolerability of regorafenib in both African and Indian population at HCG cancer speciality centre, Bengaluru between 2014 may to 2016 December. Regorafenib was prescribed in 9 patients of metastatic colorectal cancer who were in metastatic 2nd and 3rd line of treatment. Following genes are included in the 48 genomic panel (ABL1, AKT1, ALK, APC, ATU1, BRA1, CDH1, CSFIR, CTNNB1, EGFR, ERBB2, ERBB4, FBXW7, FHFR1, FHFR2, FHFR3, FLT3, GNA9, GNA11, GNAS, HNF1A, HRAS, IDH1, JAK2, JAK3, LDR, KIT, KDR, KRAS, MET, MLH1, MPL, NOTCH1, NPM1, NRAS, PDGFRα, PIK3CA, PTEN, PTPN11, RB1, RET, SMAB4, SMARCBI, SMU, SRC, STK11, TP53, VHL).

Results
The median age of 9 patients was 54 years (21-71 years). 5 patients were male and 4 patients were female, 6 patients are African and 3 were Indian. KRAS gene was found to be mutated in 6 patients and wild type in 3 patients (Table 1). Out of 9 patients, 6 have received FOLFOX-4 chemotherapy+Biological for 6 cycles and 3 patients received FOLFIRI chemotherapy+Biological for 3 cycles as 1st line treatment. Patients progressed on FOLFOX-4 were given 5 cycles of FOLFIRI. These patients received tab Regorafenib as 3rd line treatment. Patients progressed on FOLFIRI were given regorafenib as 2nd line treatment. The average duration of regorafenib was 4.1 cycle (1-9 cycles). For all patients 48 Gene panel was done, which includes extended RAS and KDR gene mutation analysis. Response in 3 months seen as PR in 2 (25%), SD in 1 (12.5%) and PD in 5 (62.5%) and 1 patient is defaulted on Regorafenib (Table 2).

With regards to safety, All patients had Grade I and Grade II toxicities. These include, Hypertension, Hyperglycemia & abnormal Liver Function Test. These are managed conservatively and no one was discontinued from treatment. No Grade III/Grade IV toxicities observed

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Whole group</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>54 (21-71 years)</td>
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<tr>
<td>Sex</td>
<td>Male 5 (56%)</td>
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<table>
<thead>
<tr>
<th>Table 1: Shows the patient demographic, mutational and treatment characteristics.</th>
<th>Frequency</th>
<th>Percent</th>
<th>Valid Percent</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>2</td>
<td>25</td>
<td>25</td>
<td>25</td>
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<tr>
<td>PD</td>
<td>5</td>
<td>62.5</td>
<td>62.5</td>
<td>87.5</td>
</tr>
<tr>
<td>SD</td>
<td>1</td>
<td>12.5</td>
<td>12.5</td>
<td>100</td>
</tr>
</tbody>
</table>
Discussion

All patients in this study have wild type KDR gene. There are 2 partial response (PR) of which 1 patient is KRAS wildtype and other is mutated. Stable disease (SD) seen in one patient with KRAS mutation. Progressive disease was observed in 5 patients and 4 of them have mutated KRAS and 1 was wild type. Because of small sample of Indian patients, response rates cannot be compared with African patients (2 patient's vs. 6 patients). KDR gene mutation occurs in tyrosine kinase domain of VEGFR2 making it a potential target for regorafenib [2]. Failure of regorafenib in the present study may be due to absence of KDR mutation. Though it is indirect evidence and hence, it requires large number of patients with KDR gene mutation to show the significant response.

Conclusion

Absence of KDR gene mutation may not respond to regorafenib treatment in MCRC. To Predict KDR gene mutation as a biomarker, large number of studies with mutated KDR gene is warranted.

References