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Clinical Response to Sorafenib in a Patient with Metastatic Colorectal Cancer and FLT3 Amplification

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Key Words
Metastatic colorectal cancer · Sorafenib · FLT3 amplification

Abstract
Background: A considerable number of patients with metastatic colorectal cancer progress after exhausting all approved standard therapies but maintain an adequate performance status and could be candidates for further treatment. We aim at reviewing our experience with sorafenib treatment of a patient with FLT3 mutation in refractory metastatic colorectal cancer. ***Methods:*** Treatment with sorafenib of a patient with metastatic colorectal cancer and FLT3 translocation who had previously been heavily treated. ***Results:*** The patient with metastatic colorectal cancer, aged 51 years, showed significant symptomatic and laboratory improvement with sorafenib treatment (400 mg twice daily). ***Conclusion:*** The presented case illustrates how an aggressive and refractory colorectal tumor may respond well to targeted therapy.

Introduction

Colorectal cancer (CRC) is the third most common type of cancer worldwide and the second leading cause of cancer-related mortality in humans [1]. At the time of the diagnosis, approximately 30% of the patients have distant metastases, which predominantly occur in the liver [1]. Surgical removal of metastatic deposits remains the only curative approach [2, 3]. However, most patients with advanced CRC will eventually die of metastatic disease, highlighting the desperate need for new and better therapies [1].

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Progress in genome sequencing technology has facilitated the identification of crucial genetic alterations that control cancer cell proliferation by constitutive activation of cell signaling/cell cycling pathways or by inactivation of critical negative regulators of these networks [4–8]. More recently, a number of antibodies and small molecule inhibitors have been developed that target particular oncogenic drivers [9–13]. These targeted agents may not work extraordinarily well in an unselected population but may induce dramatic regression in tumors harboring the target, demonstrating the concept of 'precision' medicine.

Targeted next-generation sequencing (NGS) sequences the entire coding region of a large number of preselected genes with clinical or preclinical relevance in cancer [14]. It also provides a comprehensive analysis of genes with potential therapeutic and prognostic importance, a quick turnaround time (2–3 weeks in this case), and a standardized analytics pipeline [15]. Some patients with identified potentially actionable mutations may derive clinical benefit by receiving genotype-directed therapy.

We report the case of a patient with K-RAS mutated metastatic CRC who had already progressed on all standard therapies and wanted to pursue further options. A clinical comprehensive targeted genomic profile (FoundationOne) with the goal of finding potential drug-targetable genomic alterations was requested. FLT3 amplification was identified and the patient was started on sorafenib, achieving a great clinical benefit.

Case Report

A 51-year-old, previously healthy man presented in March 2011 with bowel habit alteration. He was investigated with a colonoscopy, which revealed a stenotic adenocarcinoma of the upper rectum. Imaging staging showed metastatic lesions in the liver and lungs. However, given the obstructive symptoms, he underwent rectosigmoidectomy. Pathology was consistent with a pT3pN2 (18 out of 19 lymph nodes positive) rectal adenocarcinoma. Molecular studies revealed the presence of KRAS G12D in the neoplastic tissue. A few weeks later, the patient was started on FOLFOX. Evaluation after 4 cycles showed a partial response on the lung and liver, and at that time he underwent resection of the liver and lung lesions. He was then restarted on FOLFOX and completed a total of 11 cycles. Unfortunately, after having stopped treatment with FOLFOX following 5 months, he was found to have new pulmonary and liver lesions, local recurrence, solitary CNS metastases and multiple lymph node metastases. In order to provide better local control, he received short-course radiotherapy (5 × 500 cGy) to the pelvic area followed by surgery. A few weeks later, he underwent neurosurgery with resection of the posterior fossa lesion followed by stereotactic radiosurgery to the surgical bed. Soon thereafter, he was started on FOLFIRI and bevacizumab, achieving stable disease for 6 months with progression in multiple sites 6 months later. At that time, the patient was cachectic, with an Eastern Cooperative Oncology Group performance status of 3 and with signs of liver insufficiency with hepatic encephalopathy. Blood tests revealed a total bilirubin level of 11 mg/dl. He was then admitted to the hospital for supportive treatment, and given the lack of standard therapies and the rapid progression of the disease, hospice care was discussed. Nevertheless, we decided to order a clinical comprehensive targeted genomic profile (FoundationOne) of his tumor with the goal of finding potential drug-targetable genomic alterations. Paraffin-embedded tumor tissue was evaluated using NGS (Foundation Medicine, Cambridge, Mass., USA). Hybridization capture of 3,769 exons from 236 cancer-related genes and of 47 introns from 19 genes commonly rearranged in cancer was applied to ≥50 ng of DNA extracted from the tumor specimens and sequenced to high, uniform coverage. FoundationOne identified 6 genomic alterations (KRAS G12D, FLT3 am-

plification, BRCA1 Q1756fs*74, TP53 splice site 920-1G>T, APC E1379* and CDK8 amplification). Either sunitinib or sorafenib (both FDA-approved drugs) were suggested as therapies associated with potential clinical benefit based on the presence of FLT3 amplification. In November 2013, the patient was started on sorafenib (400 mg twice daily). Within 7 days of therapy, the patient experienced a fast improvement of the encephalopathy and his performance status. The total bilirubin levels went down from 11 mg/dl to normal levels after 30 days. Four months later, the patients presented with disease progression and died of liver insufficiency secondary the metastatic rectal cancer.

Discussion

The identification of relevant molecular targets for cancer initiation and/or progression is an important focus for the development of targeted therapies for CRC, and significant advances have recently been made as a result of projects such as the National Cancer Institute's Cancer Genome Atlas Network [16]. Patients whose tumors depend on particular targets can then be selected to avoid or minimize primary resistance to therapy.

Several critical genes and pathways important in the initiation and progression of CRC have already been identified, such as WNT, RAS/MAPK, PI3K, TGF-β, P53 and DNA mismatch repair pathways [17]. Large-scale sequencing analyses have found numerous recurrently mutated genes and a recurrent chromosomal translocation [18–20]. In order to better characterize somatic alterations in CRC, the Cancer Genome Atlas Network conducted a genome scale analysis of 276 samples, analyzing exome sequences, DNA copy number, promoter methylation and messenger RNA and microRNA expression [16]. Twenty-four genes were significantly mutated, and in addition to the expected APC, TP53, SMAD4, PIK3CA and KRAS mutations, frequent mutations in ARID1A, SOX9 and FAM123B were discovered [16]. When we requested a targeted genomic profile for the presented case, FLT3 amplification was identified and sorafenib was suggested as a potential targeted therapy.

FLT3 encodes a receptor tyrosine kinase. FLT3 mutations are the most common somatic mutations observed in acute myeloid leukemia, and their presence may be a prognostic factor for poor outcome. Activating mutations of the *FLT3* receptor gene lead to the constitutive activation of the FLT3 receptor tyrosine kinase and cause autonomous, cytokine-independent proliferation in vitro [21]. Signaling through the FLT3 pathway leads to the phosphorylation of Shc1 and Akt1 and the activation of mTOR, as well as RAS activation and phosphorylation of ERK1 and 2 [22–24]. FLT3 amplification has been reported at low levels in several tumor types, including colon and rectum adenocarcinoma (4.2%, 21/489) [25]. However, the frequency of *FLT3* gene amplification in CRC and its biological significance remain unknown. In cancer cells with activating mutations in FLT3, Flt3 inhibitors or tyrosine kinase inhibitors have been shown to be effective [26, 27]. Several Flt3 inhibitors, including sunitinib and sorafenib, have been approved by the FDA for use in other indications. These and other inhibitors are under clinical investigation in several cancer types. However, it remains unknown if the rationale for the use of these Flt3 inhibitors applies to tumors with amplifications in FLT3.

Sorafenib has shown preclinical activity against a variety of tumor types [28–32] and is a standard treatment for advanced hepatocellular and renal cell carcinomas [33, 34]. It is an orally available multikinase inhibitor that targets Raf serine/threonine kinases (Raf-1, wild-type B-Raf and B-Raf V600E), vascular endothelial growth factor receptor (VEGFR)-1, -2 and -3, platelet-derived growth factor receptor (PDGFR)-β and FLT3, c-Kit and p38 tyrosine kinases. Sorafenib has a dual action that targets serine/threonine and receptor tyrosine kinas-

es, inhibiting not only the Raf cascade, preventing the downstream mediation of cell growth and proliferation, but also the VEGFR-2, -3/PDGFR-β signaling cascade, inhibiting the activation of angiogenesis. Therefore, sorafenib acts by inhibiting tumor growth and disrupting tumor microvasculature through antiproliferative, antiangiogenic and proapoptotic effects [35–38]. Amplification of FLT3 may predict sensitivity to sorafenib, although it is unclear if high-level amplification of FLT3 results in activation. Sorafenib has been shown to inhibit activated Flt3 in preclinical studies of acute myeloid leukemia [27].

Sorafenib has already been tested in a phase IIb trial with an unselected population with metastatic CRC. Patients were randomized to sorafenib (400 mg twice daily) or placebo, combined with mFOLFOX6 (oxaliplatin 85 mg/m^2; levoleucovorin 200 mg/m^2; fluorouracil 400 mg/m^2 bolus and 2,400 mg/m^2 continuous infusion) every 14 days. Median progression-free survival for sorafenib plus mFOLFOX6 was 9.1 months versus 8.7 months for placebo plus mFOLFOX6 ($p = 0.46$). There was also no difference between treatment arms for overall survival. Subgroup analyses of progression-free survival and overall survival were performed, but showed no difference between treatment arms considering KRAS or BRAF status (mutant and wild type). However, a benefit for sorafenib cannot be ruled out in more specific patient populations, such as the presented case. In addition, a phase Ib study reported a modest response rate for the combination of sorafenib, cetuximab and irinotecan in advanced CRC [39].

The presented case illustrates how an aggressive and refractory colorectal tumor may respond well to targeted therapy. We showed that the use of targeted NGS in clinical settings is practical and can benefit patients because of the ability to define tumors genetically. Despite notable success, effective genetically targeted therapies currently remain unavailable for most patients. Moreover, some patients with potentially actionable alterations do not respond to genotype-directed therapy, highlighting the still underdeveloped understanding of the pathophysiologic implications of many genetic alterations. Systematic evaluation of the predictive value of these genomic alterations is critically important for further progress in this field.

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