Long-Term Survival with Regorafenib in KRAS-Mutated Metastatic Rectal Cancer

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Abstract
Regorafenib, an oral multikinase inhibitor, was approved in September 2012 by the US Food and Drug Administration for the treatment of patients with metastatic colorectal cancer progressing on standard therapies. Here, we describe the clinical history of a 63-year-old male patient who was treated with regorafenib in the pivotal CORRECT trial. The patient was initially diagnosed in November 2008 with nonmetastatic KRAS-mutated (exon 2, codon 12) rectal cancer. He underwent successful surgery and was treated with 5 cycles of adjuvant chemotherapy. In 2010, lung metastases (KRAS-mutated) were detected and the patient received 6 cycles of FOLFIRI plus bevacizumab. By January 2011, the metastases had progressed. The patient, who was asymptomatic with an Eastern Cooperative Oncology Group performance status of 0, was enrolled onto the CORRECT trial and received best supportive care plus regorafenib (160 mg once daily for 3 weeks of a 4-week cycle) over a period of 2 years, during which time the disease remained stable and the patient remained asymptomatic. Grade 1 anemia and thrombocytopenia were the only treatment-emergent adverse events reported. After receiving 26 cycles of regorafenib, a majority of the lung lesions progressed, and third-line palliative 5-fluorouracil, leucovorin, and oxaliplatin chemotherapy was administered. The patient died in May 2016.

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Introduction

Regorafenib (BAY 73-4506, Stivarga®) is an oral multikinase inhibitor with a distinct and wide-ranging profile of tyrosine kinase inhibition including membrane-bound and intracellular kinases that are involved in normal cellular functions, and in pathological processes including oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment. This distinct antiangiogenic profile includes inhibition of both VEGFR2 and TIE2 tyrosine kinases [1]. Regorafenib has been approved in Europe and the USA for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, anti-VEGF therapy, and, if the tumor is KRAS wild-type, anti-EGFR therapy [2, 3]. In the international, multicenter, randomized, double-blind, placebo-controlled phase III CORRECT trial, regorafenib (compared with placebo) increased the overall survival of patients with metastatic colorectal cancer who had progressed after all standard therapies [4].

The case report presented herein is of a patient that we enrolled into the CORRECT study, and for whom treatment with regorafenib permitted stabilization of his metastatic disease over 2 years, during which time the patient remained asymptomatic.

Case Report

In November 2008, a 63-year-old male patient presented with an intestinal obstruction on a computed tomography (CT) scan and was subsequently diagnosed, after resection of the primary tumor, with a KRAS-mutated (exon 2, codon 12) adenocarcinoma of the rectum at 8 cm from the anal verge. An emergency discharge stoma was performed, and 10 days later the patient underwent a low anterior resection with a coloanal anastomosis and a de-functioning loop ileostomy. Pathology diagnosis was of a well-differentiated adenocarcinoma infiltrating to the intestinal serosa. Longitudinal surgical margins were healthy (R0). There were no lymph node metastases (0/16). A chest CT scan did not show any distant metastatic lesions. From December 15, 2008 to June 15, 2009, the patient received adjuvant chemotherapy comprising 5 cycles of 5-fluorouracil (5-FU), leucovorin, and oxaliplatin (FOLFOX4 regimen).

In January 2010, while the patient was asymptomatic, radiological assessment (chest CT) detected the presence of lung lesions: a left lower lobe mass of 31 mm, 2 nodules associated with the right upper lobe (11 and 9 mm), and a left upper lobe nodule (12 mm). The lesions were found to be hypermetabolic by positron emission tomography/CT. Bronchoscopy with endobronchial biopsy of the left lower lobe mass confirmed the presence of a colorectal adenocarcinoma metastasis, which on DNA analysis was shown to have a KRAS mutation (exon 2, codon 12) and to have a microsatellite stable status. At this time, blood carcinoembryonic antigen (CEA) levels were as high as 8.2 µg/L. From February 17 to April 4, 2010, the patient received first-line palliative chemotherapy comprising 5-FU, leucovorin, and irinotecan (FOLFIRI regimen) combined with VEGF-targeted therapy (bevacizumab). Radiological assessment performed after 6 cycles of treatment showed a slight increase in the size of the lung nodules, whilst the patient remained asymptomatic. It was decided that the patient should undergo clinical and biological surveillance. A gradual elevation in CEA levels was observed from August 2010 to January 2011 (CEA levels increased from 14.0 µg/L in July 2010 to 30.3 µg/L in November 2010).
In January 2011, a new radiological assessment demonstrated progression of the patient's metastatic lung lesions; the largest lesion was recorded in the lower left lobe of 60 × 45 mm (24 × 41 mm in August 2010). The patient was then included in the CORRECT study and randomly assigned to the regorafenib arm. The patient was then 65 years old, had an Eastern Cooperative Group (ECOG) performance status of 0, and was asymptomatic, with normal renal and hepatic function. From February 16, 2011 to March 12, 2013 the patient received best supportive care and second-line regorafenib (160 mg once daily for 3 weeks of a 4-week cycle), allowing stabilization of the disease (Fig. 1). During this period, grade 1 anemia and thrombocytopenia were the only treatment-emergent adverse events recorded. After 26 cycles of regorafenib treatment, disease progression of the majority of the lung lesions was reported, and a decision was made to switch to a third-line chemotherapy comprising 5-FU, leucovorin, and oxaliplatin. The patient died in May 2016, 6 years after the diagnosis of his metastatic disease.

Discussion

We report an extraordinary outcome for a patient with KRAS-mutated metastatic colorectal cancer during 26 months of regorafenib treatment. In the CORRECT trial [4], the median duration of treatment was 1.7 months (interquartile range [IQR] 1.4–3.7). Complete responses were not reported, although 5 patients assigned to regorafenib and 1 patient assigned to placebo had a partial response, giving objective response rates of 1.0 and 0.4%, respectively (p = 0.19). Disease control (partial response plus stable disease assessed at least 6 weeks after randomization) was achieved in 207 (41%) of 505 patients assigned to regorafenib and 38 (15%) of 255 patients assigned to the placebo group. The median duration of stable disease was 2.0 months (IQR 1.7–4.0) in the regorafenib group and 1.7 months (IQR 1.4–1.9) in the placebo group. Our patient was a long-term survivor of the CORRECT trial. We hypothesize that either this patient's tumor was extremely sensitive to the drug and/or that he had favorable tumor biology, characteristics which might explain his long-term survival after the diagnosis of metastatic disease.

This current report describes the long-term efficacy of regorafenib, with 26 months of treatment with disease stabilization. The patient remained asymptomatic throughout the study period. The treatment was extremely well tolerated with only grade 1 anemia and grade 1 thrombocytopenia reported. The most commonly reported adverse events related to regorafenib such as hand-foot skin reaction, fatigue, diarrhea, hypertension, or rash were not observed [4, 5].

A recent report describes a 65-year-old woman with KRAS-mutated colon cancer that metastasized to the lung, who experienced a significant reduction in tumor size after treatment with third-line regorafenib [6]. The survival period reported for the patient in our study is much longer than would be expected for a patient with KRAS exon 2-mutated metastatic colorectal cancer. The last 5–10 years have seen unprecedented advances in the treatment of metastatic colorectal cancer. In the era when 5-FU was the sole active agent, overall survival in phase III trials was approximately 11–12 months. In the modern era, the average median survival duration has doubled, and patients routinely live longer than 2 years. This increase has been mainly driven by the availability of new active agents including chemotherapy combinations and biologically targeted agents, with median survival times reported over 24 months [7–11]. However, KRAS tumor mutations have been associated
with an aggressive biological phenotype, poor clinical behavior, and shorter survival times compared with patients whose tumors are KRAS wild-type [12–15].

To explore further who might best benefit from regorafenib treatment in the future, one possible approach would be to perform comprehensive genomic analyses in patients who demonstrate a long response (>1 year) to regorafenib treatment.

In conclusion, in this report we describe a patient with KRAS-mutated metastatic rectal cancer progressing on standard first-line chemotherapy with bevacizumab who achieved a long period of stable disease and long-term survival when treated with second-line regorafenib under the CORRECT study protocol. Second-line treatment with regorafenib in this patient, who had a good ECOG performance status, offered the possibility of further benefit from standard third-line palliative treatments after tumor progression.

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Statement of Ethics

The study was reviewed and approved by the Ethics and Research Committee of Geneva University Hospital. The study participant provided informed written consent prior to enrollment into the study.

Disclosure Statement

M.-L. Amram declares consultancy/advisory roles for Astellas, Bayer, Janssen, Sanofi, and Pfizer. A.D. Roth declares an advisory role for Bayer. X. Montet has no conflict of interest to disclose.

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Fig. 1. Computed tomography images. Stabilization of one of the target lung lesions (the left upper nodule pulmonary metastasis) from August 2010 to August 2011.